# Drug Development & Delivery

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# Advances in Polymeric Drug Delivery

The Science & Business of Pharmaceutical and Biological Drug Development

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Attempting to Speed Up Vaccine Development to Combat the Next Pandemic

**Bob Wieden**
CAPRO™: A New Advance in Polymeric Drug Delivery

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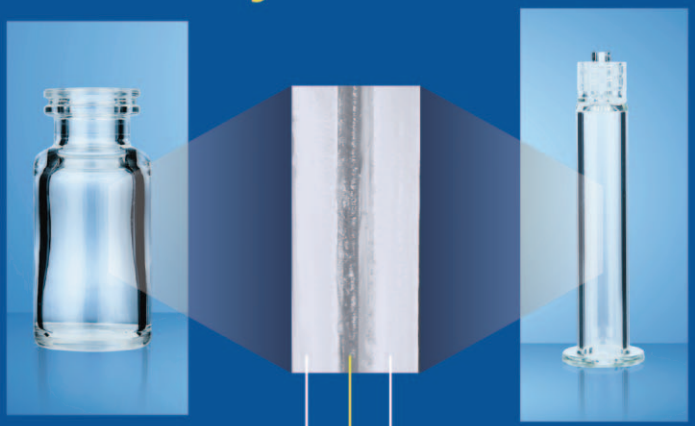

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# Manufacturing Solutions

"Maintaining production requirements of existing essential medicines, in addition to expansion of the necessary capacity to supply billions of doses of vaccine to treat the global community, have accentuated the need for agility to ensure supply reliability. Manufacturers have responded to the challenges by changing how they work in numerous ways, which will keep global supply chains prepared for years to come."

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# Polymeric Drug Delivery

"TREKKA Therapeutics flexible and versatile CAPRO polymeric drug delivery platform has the potential to enormously impact healthcare. Achieving delivery of poorly soluble drugs and biologics will enhance the efficacy of a wide range of therapeutics for the treatment of a wide range of diseases."

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# THE CREDENCE COMPANION

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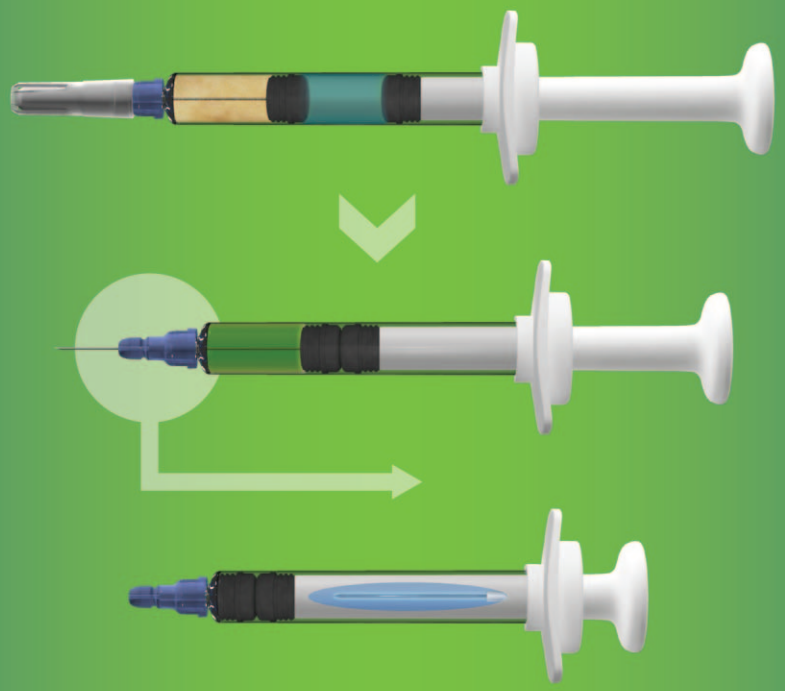

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CREDENCE MEDSYSTEMS

## Novigenix & Radbound University Medical Center Discover the First Blood-Based ImmunoTranscriptomic Biomarkers for Response to Anti-PD-1 Therapy

Novigenix SA recently announced release of the article *Whole Blood Transcriptome Profiling Identifies DNA Replication and Cell Cycle Regulation as Early Marker of Response to Anti-PD-1 in Patients with Urothelial Cancer*. Immune checkpoint inhibitors (ICIs) have become one of the main treatments for patients with metastatic urothelial cancer. Although ICIs are highly effective with durable results in some patients, only a minority respond and benefit from the therapy. There is therefore a significant unmet medical need for accurate liquid biopsy precision solutions that can select and monitor patients during ICI therapy.

Dr. Niven Mehra, Department of Medical Oncology at Radboud University, The Netherlands, said "Early blood-based response biomarkers may provide a reliable and convenient way to determine whether ICIs are effective before imaging is available, usually after 12 weeks, and can be particularly useful for those with equivocal imaging."

The study leveraged Novigenix core competencies in Immuno-Transcriptomics and machine learning for development of biomarkers and predictive algorithms. In whole blood of patients with clinical benefit, genes involved in DNA replication and cell cycle regulation were upregulated after 2 to 6 weeks of treatment. Dr. Laura Ciarloni, Director Clinical and Scientific Affairs at Novigenix, underlined "This study highlights the value of whole-blood transcriptomics platform of Novigenix, LITOseek, for generating insights into the immune response to anti-PD-1 therapy."

Dr. Sahar Hosseinian, CTO of Novigenix, added "This study demonstrates the power of whole-blood immuno-transcriptomics for discovery of clinically actionable biomarkers that support drug development. This new class of liquid biopsy precision oncology solutions may support oncologists in the treatment of urothelial cancer patients to significantly improve personalized ICI therapy and patient outcomes."

Novigenix is a precision medicine biotech providing a new understanding of the human host response to cancer and its response to therapy. The Company was founded on the vision that Immuno-Transcriptomics will bring unprecedented advances in diagnosing and treating cancer patients, leading to significant improvement in healthcare. Novigenix's unique Immuno-Transcriptomic platform enables an accelerated identification of disease specific mRNA signatures of immune cells, which combined with machine learning and predictive algorithms provide new insights into onset and progression of disease. For more information, visit www.novigenix.com

The Liquid Immuno-Transcriptomic Sequencing Platform of Novigenix, LITOseek, analyzes the gene expression modifications (mRNA signatures) induced by the host immune response to various triggers, such as onset of cancer. Disease specific algorithms are developed through application of Artificial Intelligence on patient mRNA signatures in combination with clinical and medical parameters. The LITOseek platform has been designed and optimized for development of precision oncology solutions based on the human Immuno-Transcriptome, with continuous improvement of predictive and adaptive algorithms.

## Genetron Health & IMPACT Therapeutics Announce Partnership to Drive Development of Synthetic Lethal Product Pipeline

Genetron Holdings Limited recently announced a partnership with IMPACT Therapeutics in which the two parties will cooperate together on research and development for synthetic lethal inhibitors that are based on new targets, and the development of companion diagnostic products.

"We are pleased to have reached a partnership with IMPACT Therapeutics, whose extensive pipeline products and strong data have demonstrated potential for clinical applications. Genetron Health is dedicated to accelerating patients' access to effective therapies with the adoption of precision oncology technologies," said Sizhen Wang, Co-Founder and CEO of Genetron Health. "At present, we have CAP- and CLIA-certified laboratories in China and the US. We are well-positioned to provide customized solutions for our global and domestic partners in cross-border clinical trials and companion diagnostic development. Overall, we remain committed to offering broader and better healthcare options to patients globally."

"IMPACT Therapeutics focuses on the research and development of targeted anti-cancer therapeutics that are based on synthetic lethality. We have assembled one of the most comprehensive DDR global pipeline of novel drug candidates, and are expanding to other novel synthetic lethal targets to broaden our pipeline," said Dr. Jun Bao, President and CEO of IMPACT Therapeutics. "We look forward to leveraging Genetron Health's experience and resources in the field of precision oncology, and working together with them to accelerate the research and development of new drugs, contributing to the global anti-cancer cause."

Synthetic lethality refers to the simultaneous deactivation of two, non-lethal genes that results in cell death. If specific genes can be deactivated in tumors, drugs that inhibit their synthetic lethal partner genes can target and kill cancer cells without harming healthy cells. Synthetic lethal mechanisms are expected to achieve new breakthroughs in targeted cancer therapy.

Synthetic lethal drugs possess enormous market potential. Taking PARP inhibitors (PARP is the first cancer gene to be targeted for synthetic lethal therapy) as an example, according to Evaluate Pharma, the global PARP inhibitor market will exceed US $4.5 billion by 2023, and this only includes the existing four varieties (Olaparib, Niraparib, Rucaparib, Talazoparib) that have been approved globally as of 2020.

Genetron Holdings Limited is a leading precision oncology platform company in China that specializes in cancer molecular profiling and harnesses advanced technologies in molecular biology and data science to transform cancer treatment. The company has developed a comprehensive oncology portfolio that covers the entire spectrum of cancer management, addressing needs and challenges from early screening, diagnosis and treatment recommendations, as well as continuous disease monitoring and care.

IMPACT Therapeutics is a biopharmaceutical company dedicated to the discovery and development of targeted anti-cancer therapeutics based on synthetic lethality. IMPACT Therapeutics has assembled one of the most comprehensive DNA damage response (DDR) global pipeline of novel drug candidates generated by in-house discovery efforts and is expanding to other novel synthetic lethality targets to broaden its pipeline.

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## Credence MedSystems Secures $39.9 Million Financing to Enable Scaling of Innovative Drug Delivery & Connected Health Systems

Credence MedSystems, Inc. recently announced it has closed a funding round with gross proceeds of $39.9 million. Sources of funding include strategic investments from Novartis Pharma AG, Molex Ventures LLC as well as additional investors.

The investment will be directed toward scaling of production capacity for the Credence Companion® and Dual Chamber Reconstitution Systems as well as development of other members of the company's platform of innovative drug delivery systems, including its connected health portfolio.

"The funding comes at a great time as we take the manufacturing of our Companion and Dual Chamber systems to the next level to meet pent-up demand in the market," stated John Merhige, Credence's Chief Commercial Officer.

Jeff Tillack, Credence's Chief Operating Officer, added, "Our immediate focus is on implementing the production capacity to support our customers' needs, including GMP production for clinical use."

Credence's lead products are the Companion® Safety Syringe System and the Dual Chamber Reconstitution System, which provide critical usability and safety features to end-users along with operational efficiencies to pharma manufacturers. Additionally, the products enable pharma manufacturers to leverage sustainability advantages stemming from the reduced use of plastic and smaller footprint compared to conventional approaches.

Funding also supports acceleration of Credence's connected health programs. The Credence Connect™ Auto-Sensing Injection System brings digital connectivity to any syringe, allowing critical information about the injection to be automatically captured and transmitted to a smart phone and the cloud. The Connect has the potential to impact chronic disease management and clinical trial compliance.

Credence MedSystems is an innovator 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 reuse 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. Metered dose systems and other novel devices address the needs of specific therapeutic markets such as ocular therapies and cosmetic applications. For more information, visit www.CredenceMed.com.

## SomaLogic Announces Strategic Collaboration With UPMC to Tailor Clinical Care Through Proteomics Technology

SomaLogic recently announced a strategic collaboration with leading health system UPMC to explore how the large-scale study of proteins and their functions in the body can effectively be used in clinical care.

"As part of our commitment to investing in translational science that significantly improves the lives of patients, we are evaluating whether a proteomics approach can help clinicians identify patients at the highest risk for major health events, like heart attack or stroke. That will allow us to better target interventions and care," said Suresh Mulukutla, MD, an interventional cardiologist at UPMC and Director of Analytics for the UPMC Heart and Vascular Institute.

As part of the agreement, UPMC and SomaLogic will establish a collaboration to promote the use of proteomic data in building healthier communities, improving patient care and reducing healthcare costs. The collaboration will include clinical research and development projects that establish the groundwork for use of proteomics as part of the larger vision for modern healthcare. The work planned at UPMC and insights gained may enable providers to make decisions based on an individual's unique proteomic signature, reflecting certain indicators used for determining their real-time health status and disease risk.

"Working with UPMC, a leading innovator in healthcare, allows us to evaluate together the value of proteomics as a tool for precision medicine and a means for clinicians in the future to more accurately assess risk and tailor care for their patients," said SomaLogic Chief Executive Officer Roy Smythe, MD.

"UPMC is committed to supporting innovative healthcare technologies with the goal of providing life-changing medicine to our patients and communities," said Matthias Kleinz, Senior Vice President and Head of Translational Sciences at UPMC Enterprises. "With SomaLogic, we will explore the impact of its proteomics technology on optimizing therapy selection and resource allocation across a large integrated health system like UPMC."

The agreement with UPMC is part of SomaLogic's SomaSignal Proteomics for Precision Medicine Initiative, the first large-scale, clinically focused partnership effort aimed at equipping healthcare providers with the power of proteomic technology to inform decisions at the point of care. SomaLogic can run approximately 7,000 protein measurements on a single 55-microliter plasma or serum sample. The company has run more than 450,000 samples to date.

SomaLogic seeks to deliver precise, meaningful, and actionable health-management information that empowers individuals worldwide to continuously optimize their personal health and wellness throughout their lives. This essential information, to be provided through a global network of partners and users, is derived from SomaLogic's personalized measurement of important changes in an individual's proteins over time. For more information, visit www.somalogic.com.

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## ProQR Announces Axiomer RNA Editing Licensing & Research Collaboration With Lilly

ProQR Therapeutics N.V. recently announced a global licensing and research collaboration with Eli Lilly and Company (Lilly) focused on the discovery, development, and commercialization of potential new medicines for genetic disorders in the liver and nervous system. The companies will use ProQR's proprietary Axiomer RNA editing platform to progress new drug targets toward clinical development and commercialization.

ProQR's unique Axiomer platform technology enables the editing of single nucleotides in RNA in a highly targeted and specific manner. The technology is based on editing oligonucleotides, or EONs, designed to recruit endogenous ADAR enzymes (Adenosine Deaminases Acting on RNA) to a selected target adenosine in a disease associated RNA. ADAR then induces the conversion of the target adenosine (A) into inosine (I). The conversion from A to I is effectively an A to G change, as inosine in RNA is interpreted as a guanosine (G). This technology could be applied to potentially reverse the more than 20,000 G to A mutations in the human population that are known to cause disease.

"RNA editing is an exciting emerging technology, which allows transient, reversible editing, which in some indications may be an extremely attractive therapeutic approach" said Andrew C. Adams, PhD, Vice President for New Therapeutic Modalities at Lilly. "Through this collaboration with ProQR, we hope to utilize this technology to unlock novel treatments to improve the lives of patients across a spectrum of diseases."

"This partnership with Lilly, a leader in RNA therapeutics, is an important validation of our Axiomer RNA editing platform, and expands the application of our technology beyond our core therapeutic area focus of genetic eye disease, to potentially benefit patients with metabolic and nervous system disorders." said Daniel A. de Boer, Founder and CEO of ProQR. "Additionally, this partnership further strengthens our financial position."

"Building from our deep scientific expertise in RNA therapies and specifically oligonucleotides, our Axiomer RNA base editing platform is uniquely positioned to target a wide range of diseases in a highly specific manner," said Gerard Platenburg, Chief Innovation Officer of ProQR. "Our approach uses the cell's own editing machinery to make specific single nucleotide edits in RNA to reverse a mutation. With broad applicability, and a leading patent portfolio in the ADAR editing space, this platform represents an important strategic opportunity and has significant potential to target diseases otherwise thought untreatable."

The companies will collaborate to develop up to five targets. Under the terms of the agreement, ProQR will receive $50 million consisting of an upfront payment of $20 million, as well as an equity investment in its ordinary shares of $30 million. ProQR is also eligible to receive up to approximately $1.25 billion for development, regulatory and commercialization milestones, as well as tiered royalties of up to mid-single digit percentage on product sales.

## Longeveron Partners With Kinesiometrics to Create & Implement Cutting-Edge Smart Phone App to Measure Physical Responses to Cell Therapy

Longeveron Inc. has entered into an agreement with Kinesiometrics Inc., to provide a cutting-edge, digital data-driven solution for objective real-time measurement of functional capacity and quality of life in Longeveron's clinical studies. The data is accessible to Longeveron and recipients of Lomecel-B via an Application downloadable on the subjects' mobile phones.

Longeveron recently announced the results of a Phase 2b Aging Frailty study, which showed that frail subjects (average age for study was 75.2 years) with impaired mobility could walk nearly 50 meters further 180 days after a single intravenous infusion of Lomecel-B (200 million Lomecel-B group; $p=0.0065$). This increase was durable, persisting through 270 days (200 million Lomecel-B group change from baseline 47.9 meters; $p=0.0115$, and $p<0.0077$ compared to placebo). By comparison, the placebo-treated subjects change from baseline at 180 days and 270 days was 8.0 meters ($p=0.5371$) and -15.5 meters ($p=0.2728$), respectively.

Kinesiometrics will provide Longeveron with a patented Software as a Solution (SaaS), mobile-phone based platform that can collect not only years of historical data regarding a subject's activity levels via steps, distance walked, flights climbed and energy expenditure, but also real-time response information for comparison of activity level changes pre- and post-Lomecel-B infusion. This vital data may be used to understand and gauge outcomes of treatment regimens, and information is presented in an easy to understand and compelling graphical format. With the Kinesiometrics technology, activity levels can be provided continuously, rather than relying solely on single time points throughout the follow-up period. This could provide rapid understanding of the effect of Lomecel-B and has the potential to reduce the number of protocol-specific visits a research subject needs to make to the clinic.

"Both walking speed and walking distance are highly accurate clinical indicators of overall health in older people, as well as powerful predictors of survival," said Dr. Kevin Ramdas, Director of Clinical Affairs at Longeveron. "With this new tool, we will get a richer and more comprehensive understanding of a subject's functional performance before and after infusion with Lomecel-B."

Dr. Michael Wang, a co-founder of Kinesiometrics and Chief of Neurosurgery at the University of Miami Hospital commented, "We have been looking for a partner that understands the need to use novel and modern digital methods to accelerate how patient outcomes are measured. Longeveron understands the core value of using data visualization that allows clinicians to identify critical inflection points and setbacks during a patient's recovery phase, and we look forward to working with Longeveron to achieve the goal of helping patients increase in their functional capacity and quality of life."

## ABITEC Corporation & Larodan AB Announce Brand Refresh After Successful Integration of the Two Companies

ABITEC Corporation, an ABF Ingredients company, recently announced in July 2020 the acquisition of Swedish manufacturer and international marketer of state of the art, high-purity research grade lipids, Larodan AB. After several months of virtually onboarding the company, ABITEC is anxious to announce the completion of a full integration strategy welcoming Larodan AB into the ABITEC family. In addition to the advanced technologies and innovative breakthroughs that Larodan is contributing, this relationship will now be sealed with a visual branding refresh to even further strengthen the connection and presence in the market.

As part of this transition, ABITEC felt it was important to maintain both brands but find a way to align them visually. Jeff Walton, CEO at ABITEC comments, "The goal of this change for ABITEC and Larodan was to not compromise current brand strength and identity but give each brand a refresh and create commonality among the two. This process would complete a successful integration of the two companies and help present our new collaboration to the world in a consistent and unified manner." The approach started with identifying existing similarities and utilizing specific aspects of each separate brand to create a synergistic look and feel. Since both brands already shared a common color that seemed to be the natural place to start. Amanda Coulter, Marketing Manager ABITEC comments, "Incorporating certain features of each brand image into the final design was an important part of the process. It was truly a unified approach and quite reflective of the strong team environment that ABITEC and Larodan have already built." Mimicking the rounded edges and feel of the Larodan logo, while incorporating additional colors from the ABITEC logo presented a great design opportunity. The result gave each company a refreshed look while visually connecting them and keeping the integrity of their name and brand in the marketplace. After many months of brainstorming and collaboration ABITEC and Larodan are ready to introduce their new "improved" branding.

ABITEC Corporation is part of ABF Ingredients and is headquartered in Columbus, Ohio, US with two manufacturing sites in the Midwest. ABITEC specializes in the manufacturing and distribution of specialty lipid ingredients for use in the pharmaceutical, nutraceutical, and specialty chemical markets.

Larodan develops, manufactures and markets a comprehensive range of high purity lipids for the international market. They serve customers throughout the world, directly and in collaboration with highly competent distribution partners. Their aim is to be the optimal partner for lipid related research, irrespective of the customer's need or location.

ABF Ingredients is a division of Associated British Foods that focuses on high value ingredients for both food and non-food areas and comprises a range of ingredient companies which include AB Enzymes, Ohly, PGP International, and SPI Pharma. The group has established strong market positions in cereal specialties, enzymes, esters, extruded ingredients, specialty lipids, specialty powders, specialty flours, yeast extracts worldwide.

## BD Completes Study Investigating Performance of Glass Prefillable Syringes (PFS) in Deep Cold Storage

BD (Becton, Dickinson and Company) (NYSE: BDX), a leading global medical technology company, completed a preliminary study investigating the impact of deep cold storage (-20°C and -40°C) on glass PFS.

While traditional vaccine formulations are commonly stored up to about 2°C-8°C, new vaccine formulations – including those for mRNA – require much colder storage for over a long period of time to ensure drug-product shelf-life and potency [1][2]. Such low temperatures can induce changes in container dimensions, phase transition – liquid to solid and vice versa – and thermal shock. This could compromise the functional performance of the delivery system and Container Closure Integrity (CCI). BD began its investigation on the impact of deep cold storage on glass PFS as soon as information regarding the deep cold storage requirement for mRNA COVID-19 vaccines became available in 2020.

"PFS are a known factor in addressing the complexity and costs of vaccine administration. They have been shown to significantly reduce time and labor associated with drug preparation compared to vial formats [4], and they support dose sparing [5]" said Bruno Baney, Vice President of R&D for Pharmaceutical Systems at BD. "This study confirms the promising opportunity we have to apply our leading scientific capabilities to develop innovative delivery solutions for our customers now and in the future. We're encouraged by these results and look forward to partnering with pharmaceutical companies to further advance PFS in deep cold conditions."

Following its completion of this study, BD anticipates that BD glass barrel PFS systems should be suitable for use when storage temperatures of -20°C and -40°C are required.

BD is committed to a science-driven approach to innovating and testing delivery solutions for novel therapies developed by our pharmaceutical partners – particularly as the fight against COVID-19 continues. BD is also enhancing its manufacturing capacity and technology for PFS and advanced drug delivery systems with previously announced plans to invest $1.2 billion over four years.

BD is one of the largest global medical technology companies in the world and is advancing the world of health by improving medical discovery, diagnostics and the delivery of care. The company supports the heroes on the frontlines of health care by developing innovative technology, services and solutions that help advance both clinical therapy for patients and clinical process for health care providers. BD and its 70,000 employees have a passion and commitment to help enhance the safety and efficiency of clinicians' care delivery process, enable laboratory scientists to accurately detect disease and advance researchers' capabilities to develop the next generation of diagnostics and therapeutics. BD has a presence in virtually every country and partners with organizations around the world to address some of the most challenging global health issues.

# DEVICE DEVELOPMENT

## Selecting Drug Delivery Systems for Higher Doses, Higher Viscosities & Lower Risk

By: Nicolas Bralet and Megan Lan, MBA, MA

### INTRODUCTION

The development of new parenteral biologics with high-volume, high-viscosity formulations (> 1 mL, >15 cP) is triggering the need for devices that can deliver these therapies with the ease, safety, and low injection time required for self-injection.[1-3] As these formulations come to market, pharmaceutical and biotech companies must make critical device choices from an array of largely unproven options.[2] The following discusses how companies can de-risk their device selection as they bring this new generation of high-volume, high-viscosity biologics to market.

### IDENTIFYING SOURCES OF RISK IN COMBINATION PRODUCT DEVELOPMENT

Particularly risk-prone areas of combination product development involving a primary container and secondary packaging are performance and safety. Fundamental sources of risk include incompatibility with the drug or primary container, or failure to meet usability requirements. One consequence associated with poor selection of a new injection device could be missed regulatory milestones leading to a delayed launch and the associated lost revenue. A second consequence is the potential for high reject rates during development and industrial scale-up, potentially leading to higher costs or delays. Biopharmaceutical companies launching high-volume or high-viscosity formulations must adopt strategies and plan ahead to reduce these risks.

### THE LIMITS & TRADEOFFS OF EXISTING SELF-INJECTION SYSTEMS

Autoinjectors and ergonomically optimized manual injectors are two delivery technologies often chosen for fixed-dose biologics given by self-injection. Some drugs are offered in both delivery formats, reflecting a variety of market needs and user preferences.[4] Auto and manual injectors each offer a different set of advantages and tradeoffs to end users and biopharmaceutical companies. Both technologies include ergonomic features that can mitigate challenges in delivering self-injections, such as high injection force, patient discomfort, and pain perception.[1,4,5] Both technologies also offer needle protection. Autoinjectors can help patients who lack the strength or dexterity to inject; however, not all autoinjectors are capable of delivering higher viscosities (>15 cP).[4] Manual injection systems allow users to control the speed of injection and may be able to handle higher viscosities, but they typically entail more steps for end users, and require greater force to operate, compared to autoinjectors.[6-8]

### RECONCILING COMPETING DESIGN REQUIREMENTS

Given the relative lack of commercialized delivery solutions in the 2 mL and greater, high-viscosity space compared with the ≤1 mL space, biopharmaceutical companies developing combination products with drug delivery devices face important challenges, especially because increases in volume and viscosity may

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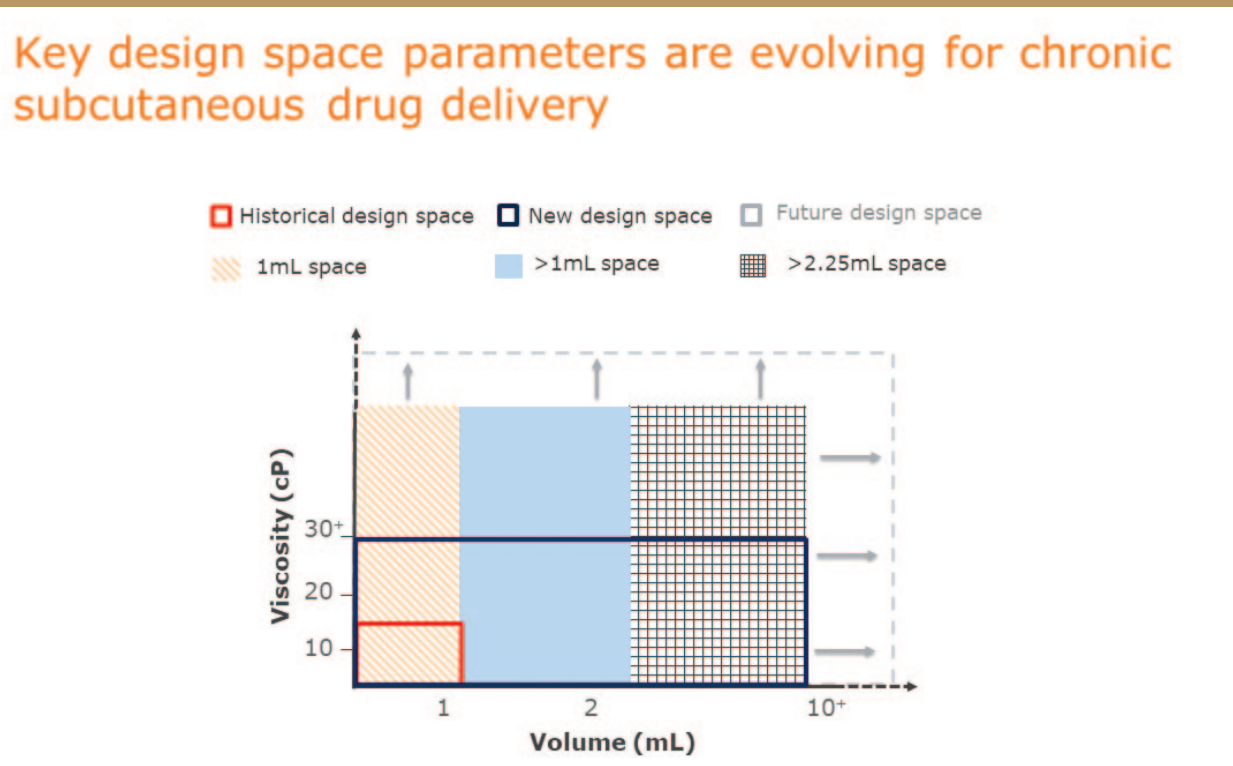
## FIGURE 1




push device design constraints towards unacceptable limits (Figures 1 & 2).[2] Competing requirements, such as injection time, injection force, ergonomics, patient comfort, and system reliability thus provide a formidable challenge for delivery system designers.[3,5,9,10] For example, to achieve an acceptable injection time with a higher volume or viscous solution, a higher injection force is often required, which in turn must be reconciled with system reliability over the intended shelf life. A higher injection force may be achieved by increasing the spring force, resulting in greater pressure within the system, which may challenge performance over the shelf life – elevating the importance of integration among components as a critical factor in achieving reliable system performance. Higher volume or higher viscosity drugs can increase the system integration challenge.

Further complicating device selection and integration is the development stage at which the primary container is chosen, typically before Phase 3, to allow time for stability testing, and prior to development of the delivery system.[11]

The primary container serves important functions, including storing and aiding delivery of the drug product. Therefore, the primary container should not only be compatible with the drug product, but it should also enable the delivery system (such as an autoinjector) to meet delivery requirements. To maintain maximum flexibility in the context of a rapidly evolving market for biologics, biopharmaceutical companies may wish to select a primary container and stopper that work well with a number of secondary delivery systems to help support lifecycle management, or to leverage a single packaging or delivery platform for multiple drug products. Unfortunately, not all primary containers and stoppers are compatible or well-integrated with complex self-injection systems.[9]

Biopharmaceutical companies will face some or all of these uncertainties as they define new systems to deliver their high-volume or high-viscosity formulations. Preventable device-related pressure points that could lead to delayed timelines include the following:

- Poor performance or reliability of the combination product caused by poor fit at component interfaces or degradation over time;
- Failure to achieve regulatory approval on time, due to issues with combination product functionality for its intended use; and
- High reject rate during industrial scale-up, leading to project delays while resolving the problem.

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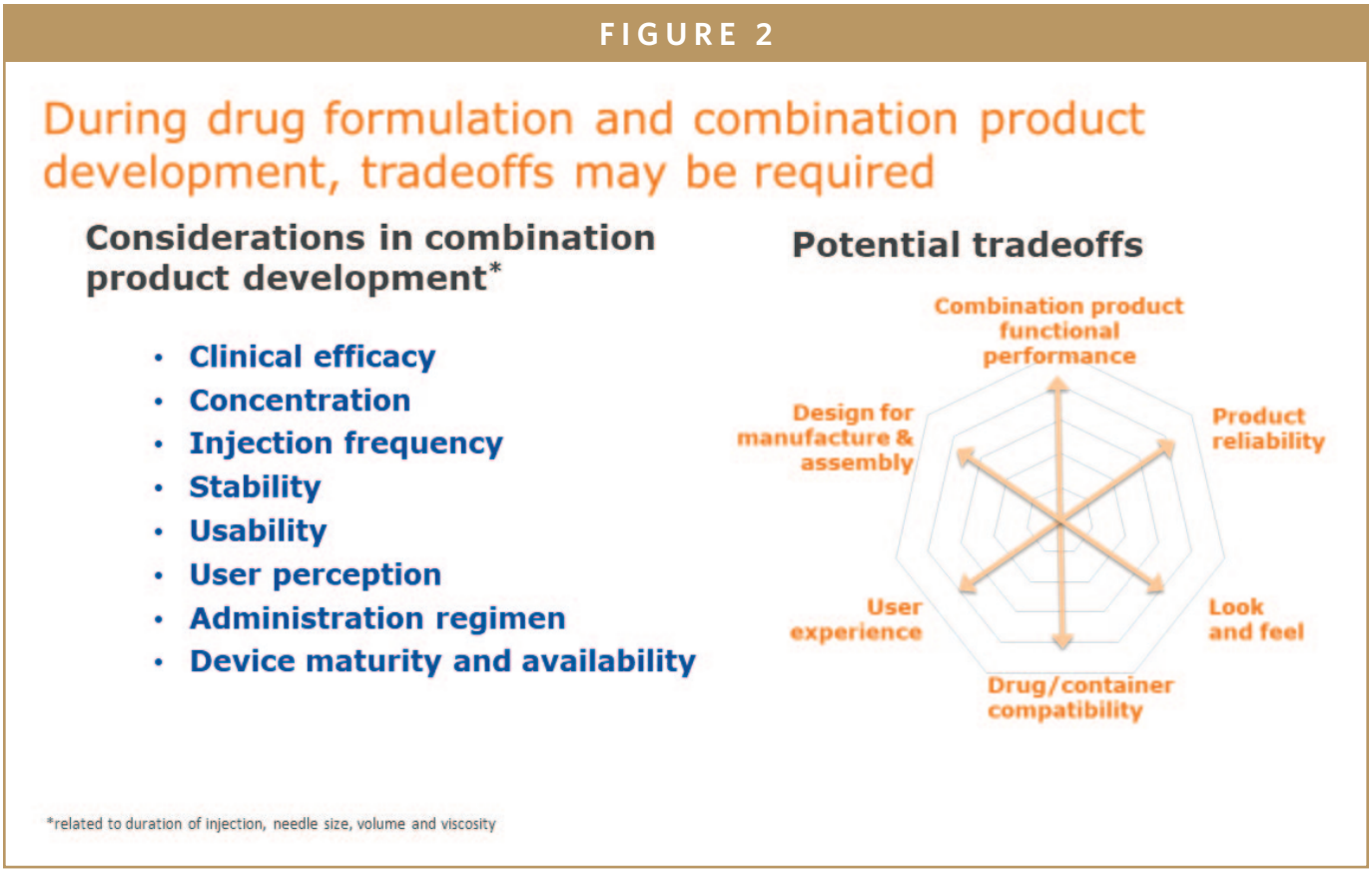
FIGURE 2




## DE-RISKING DELIVERY DEVICE DEVELOPMENT - BEST PRACTICES

There are a number of steps that can help de-risk the process of choosing the primary container and the delivery system for higher volume or higher viscosity biologics.

### Anticipate

Consider all drug delivery requirements early in development. This includes target tissue, frequency of administration, dose volume and viscosity, patient capabilities and preferences, market standards for drug administration, drug-container compatibility, primary container geometry, and fit with desired delivery systems.

### Consider All Requirements Up Front

Having an incomplete picture of key requirements for both the primary container and the delivery system can cause challenges later in development - in Phases 2b or 3, registration, launch, and life cycle management - which can be difficult to resolve while holding to both timeline and budget.

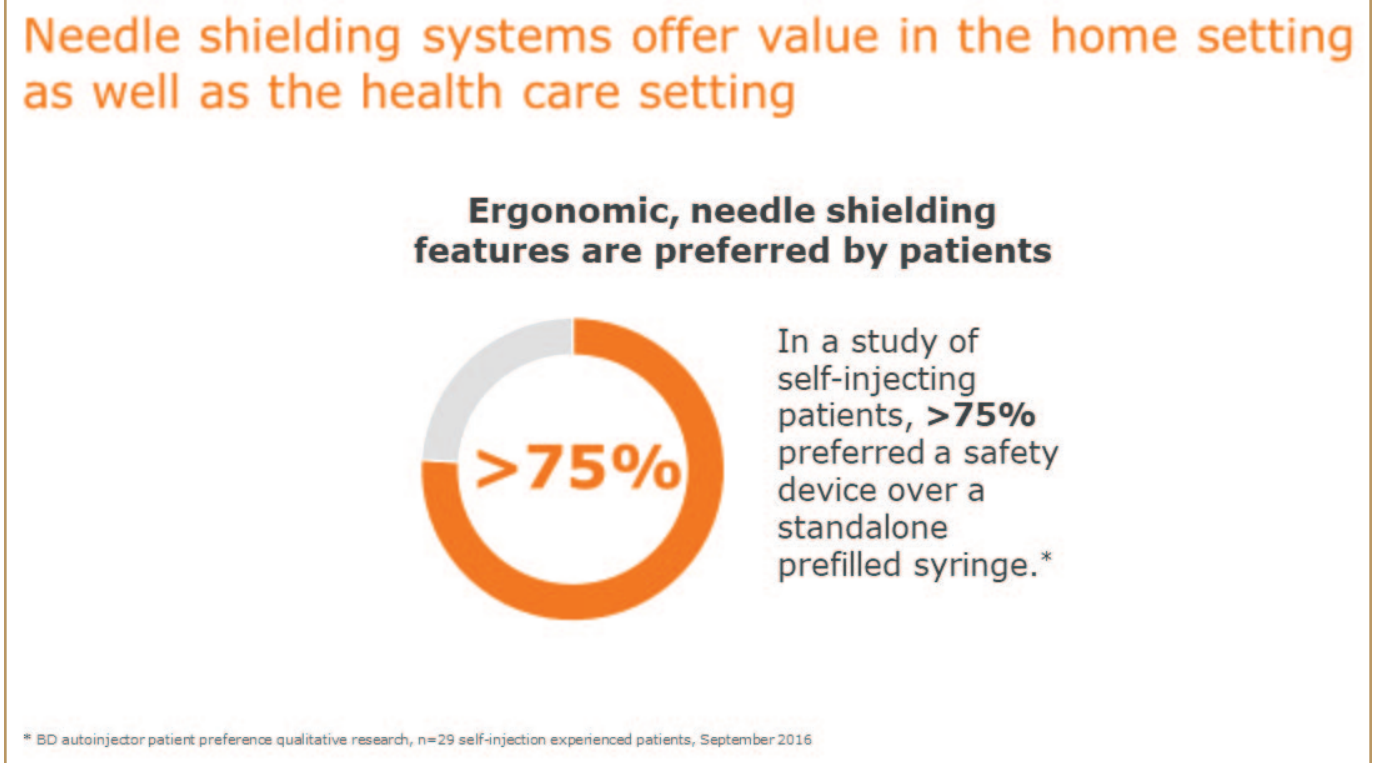
### Choose an Experienced Device Development Team

The core project team should be well connected and should include cross-functional representation, such as formulations, primary packaging, delivery device, commercial, clinical, quality, regulatory, pharmaceutical development, medical affairs, and manufacturing that can ask insightful and experience-based questions and drive robust decision making throughout product development.

### Select Critical Components of the Combination Product Based on Combined Requirements

Testing is conducted using the full system consisting of drug, primary container, stopper, and delivery system. Fit and functionality between the various constituents should be carefully evaluated for performance and reliability before the selection of components is finalized. Unfortunately, allowing sufficient time for thorough evaluation is not always possible due to the complex and iterative nature of system evaluations. Some parameters are often fixed (eg, dose volume and viscosity, or prefillable syringe type, if selected in early Phase 2), while others are not. If the delivery system doesn't function as intended, components may need to be adjusted or replaced or, in extreme cases, selection of an entirely different system may need to occur, thereby affecting the project timeline and budget. In addition, parts may come

FIGURE 3




from multiple suppliers, requiring a potentially more intensive effort to coordinate system level evaluations.

## CHOOSING A PARTNER TO HELP MANAGE COMPLEXITY

Project complexity and the risks associated with developing combination products for biologics may be reduced by partnering with a device manufacturer with a high level of primary container and secondary packaging experience and who understands the most sensitive integration points. Risk can be further reduced if that partner adopts a "quality by design" philosophy in developing primary containers and delivery systems that function together. Beyond effective integration, data and support services are also critical components of success in developing combination products. For biopharmaceutical companies, having additional data that complements the combination product regulatory submission can reduce the quantity of testing required and can also provide assurance of meeting delivery system requirements, while helping to de-risk the overall development process.

## DRUG DELIVERY SYSTEMS: A CHECKLIST FOR SUCCESS

What are the components of a successful biologic drug delivery system? First, it should be user-friendly (Figure 3), meaning that it has been successfully tested with diverse target user groups, including patients with varying capabilities and characteristics, if intended for self-injection.[3] A drug delivery system should also incorporate experience from commercialized solutions that are broadly used in the market, which can potentially reduce risk when incorporated into combination products. Finally, the system should be robust, effectively integrated, and compatible with established primary containers for biologics. Addressing these criteria can increase the likelihood of compatibility with the drug, and of the combination product's reliable performance throughout launch and commercialization.

## BD ULTRASAFE PLUS™ 2.25 ML PASSIVE NEEDLE GUARD: PART OF A FULL-SOLUTION APPROACH FOR BIOLOGICS

BD UltraSafe Plus™ 2.25 mL is now available to address biologic drug delivery needs, and together with prefillable syringes is capable of delivering up to 2 mL and 30 cP solutions.[8] An ergonomic manual injection system with passive needle shielding, its design is similar to the BD Ul-

traSafe Passive™ and BD UltraSafe Plus™ 1 mL needle guards, of which more than 1 billion units have been sold since 2010.[12] The BD UltraSafe™ product family has a history of commercial use by both healthcare providers and patients, and has been used in a wide variety of therapeutic settings.[12]

A human factors validation study has shown that injections given with BD UltraSafe Plus™ 2.25 mL can be successful and sufficiently acceptable up to 2 mL and 30 cP*.[7] The study, conducted with a broad range of users including dexterity-challenged patients, found the system to be usable across all studied viscosities. There was no decline in usability results from 1 cP to 18 cP and up to 30 cP. With a 30 cP solution, the rate of full-dose delivery was still high, at 95% of injections fully delivered. Upon full-dose delivery into an injection pad, the needle guard was consistently activated. More than 95% of users were confident or very confident that the activated BD UltraSafe Plus™ safety mechanism would protect them from needlestick injuries**.

* When tested with a standard syringe for viscous biologics, the BD Neopak™ 2.25 mL Glass Prefillable Syringe with a 27G special thin wall 12.7 mm needle.

** Rated on a Likert scale of 1 to 6, from "Not At All Confident" to "Very Confident."

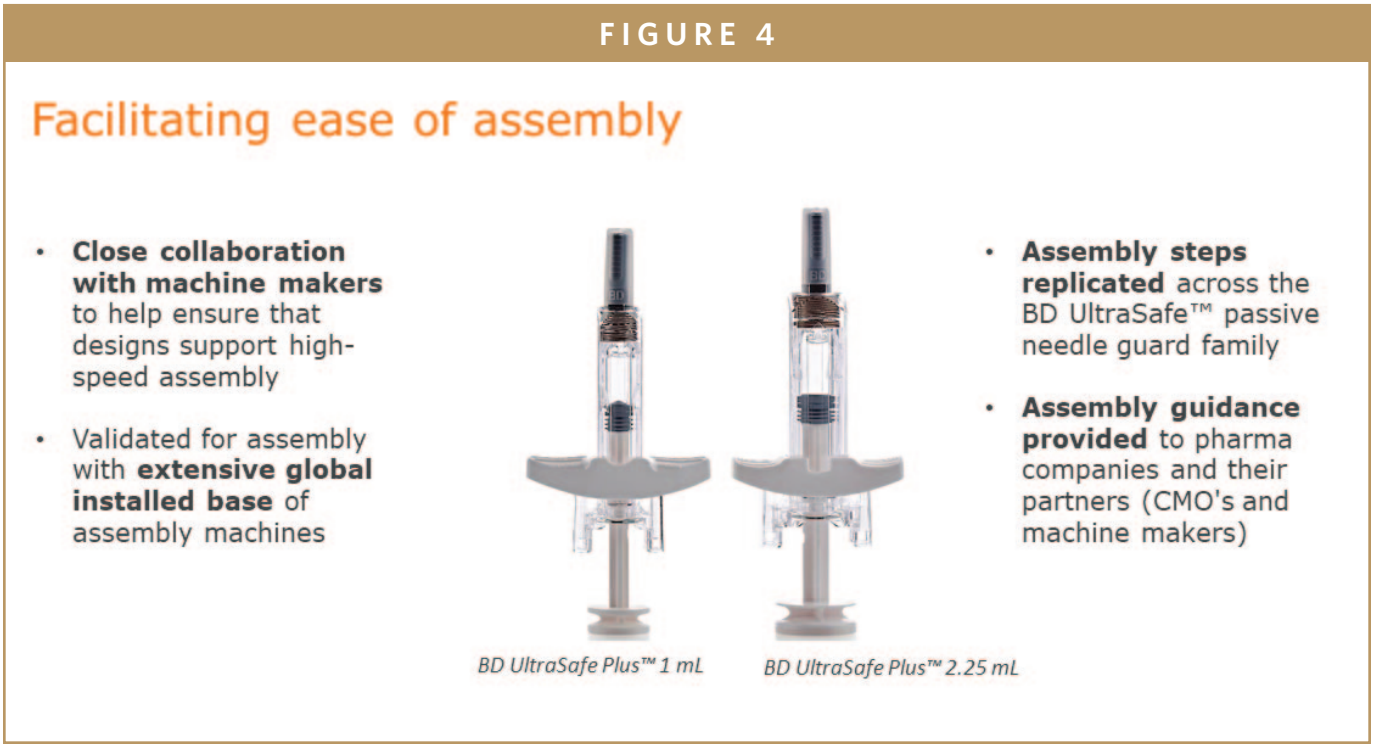
## COMPATIBLE WITH A LEADING PRIMARY CONTAINER FOR BIOLOGICS

BD UltraSafe Plus™ 2.25 mL is compatible with a platform solution for biologics, the BD Neopak™ 2.25 mL prefillable syringe.[13] The BD Neopak™ Glass Prefillable Syringe platform benefits from an optimized manufacturing process to become BD's highest standard in prefillable syringes, helping to de-risk biologic drug development and time to market. Through quality by design, process control, and system interface specifications, BD Neopak™ supports autoinjector compatibility.[14-16] This may help enable cost and time savings in developing a single primary container that may fit with multiple systems, when several different secondary delivery formats may be desired. The BD Neopak™ 2.25 mL provides the flexibility required to be leveraged as a platform solution.

Additionally, the BD Neopak™ platform technology is designed to ensure robust compatibility and reliable performance with BD self-injection systems, such as the BD Intevia™ 1 mL and 2.25 mL two-step Disposable Autoinjectors ***.

*** BD Intevia™ 2.25 Disposable Autoinjector is a product in development; some statements are forward looking and are subject to a variety of risks and uncertainties. BD Intevia™ Disposable Autoinjectors are device components intended for drug-device combination products and not subject to FDA 510(k) clearance or separate EU CE mark certification.

**FIGURE 4**



## ULTRA-THIN WALL, 8 MM NEEDLE TECHNOLOGY – ENHANCING BD ULTRASAFE PLUS™ PERFORMANCE

The newly developed BD Neopak™ XtraFlow™ Glass Prefillable Syringe† been designed to improve the subcutaneous delivery of drugs with high viscosities by enhancing the injection experience through a reduction in injection effort or time.[7,17,18] BD recently tested the benefits of the BD UltraSafe Plus™ 2.25 mL needle guard in combination with the BD Neopak™ XtraFlow™ (8mm, 27G ultra-thin wall needle) prefillable syringe.[19] More than 120 injections of a 30 cP solution were simulated in a human factors study. Directional results indicate that subjects perceived a reduction in the force needed to push the plunger during injection when using BD UltraSafe Plus™ 2.25 mL and BD Neopak™ XtraFlow™ 2.25 mL together. The percentage of users who rated the plunger as "easy or very easy to push" more than doubled from 15% (standard syringe) to 41% (BD Neopak XtraFlow™ syringe)†† UltraSafe Plus mL passive needle guard, when combined with BD Neopak™ XtraFlow™ prefillable syringe, may provide a better experience for end users, including self-injecting patients.

† Neopak™ XtraFlow™ Glass Prefillable Syringes are products in development; some statements are forward looking and are subject to a variety of risks and uncertainties.

†† Rated on a Likert scale of 1 to 6, from "Very Difficult" to "Very Easy."

## REDUCE YOUR RISK FROM DEVELOPMENT TO SCALE-UP

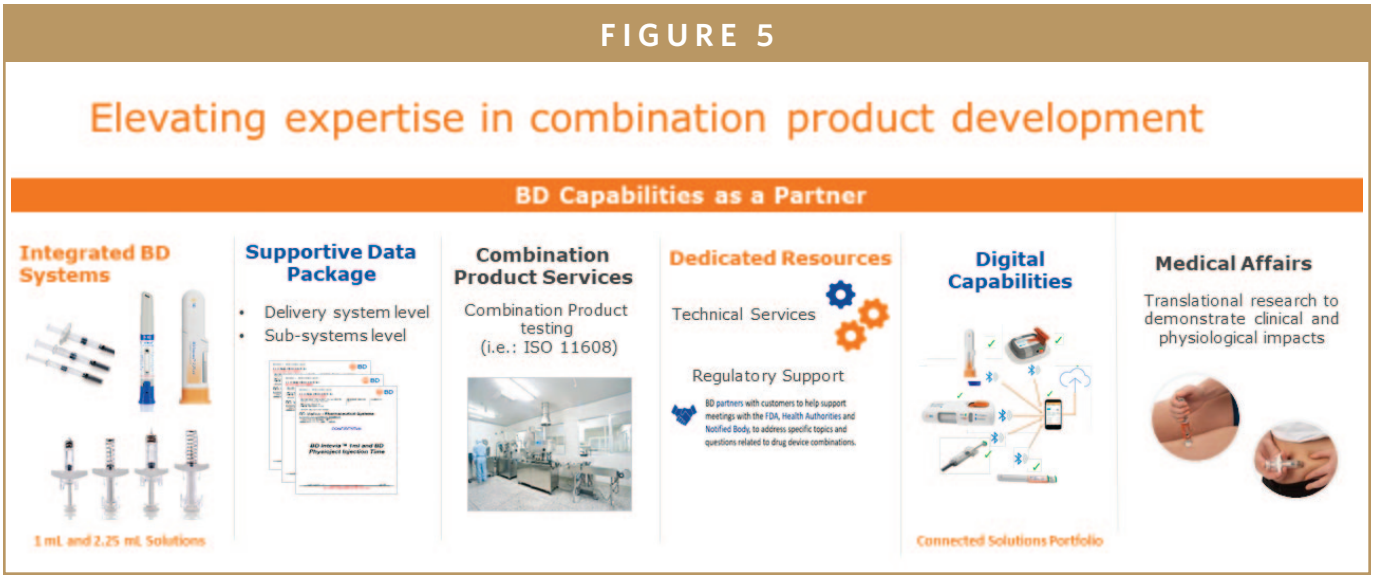
At BD, we leverage our primary container expertise and extensive experience in prefillable syringes to develop drug delivery systems that perform reliably against stringent performance standards and requirements.[20] Incorporating this expertise into combination product development can reduce the likelihood that integration issues will occur during development, at scale-up, or after commercial launch.

BD undertakes important steps that help to ensure that the assembly process of combination products involving several different components can be scaled up with the requisite speed and quality, while minimizing waste. Careful attention to the design of the assembly process addresses an important risk point for biopharmaceutical companies that depend on the smooth integration of the primary container and secondary delivery system at speed and during industrialization.[21] With the design of BD UltraSafe Plus™ 2.25 mL, BD aims to decrease assembly risk for our biopharmaceutical partners to help shorten the high-speed assembly start-up curve, reduce costs, and lower the risk of on-market failures (Figure 4).

## BD: A FULL-SOLUTION PARTNER

BD offers services and data that complement biopharmaceutical partners' combination product development capabilities and expertise (Figure 5). This includes assembly guidance, combination product testing services, designs validated with thorough and rigorous human factors testing, validated platform IFUs (instructions for use), and access to small development quantities and regulatory-compliant data packages through the BD

FIGURE 5



PartnerPath™ program.[22] These services aim to help our partners limit development complexities related to primary containers and secondary delivery systems, and to reduce risk to timelines and cost.

## EXTEND YOUR OPTIONS WITH THE BD ULTRASAFE PLUSTM 2.25 ML PASSIVE NEEDLE GUARD

BD UltraSafe Plus™ 2.25 mL passive needle guard is an ergonomic accessory for manual injection that can complement biopharmaceutical companies' total offering to address patients' needs in both manual injector and autoinjector formats, and can help support the market launch of viscous (up to 30 cP) 2 mL drug therapies. With extensive experience in the end-to-end integration of combination products and a platform approach based on BD Neopak™ 2.25 mL, BD offers capabilities, experience, and a suite of solutions, including the BD UltraSafe Plus™ 2.25 mL passive needle guard, to companies seeking to minimize the risk and optimize the success of their high-volume, high-viscosity biologic therapies. ◆

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**Nicolas Bralet** is Worldwide Safety Platform Leader at BD Medical-Pharmaceutical Systems, responsible for the performance of the safety platform. He defines and implements the safety strategy, the portfolio of product and process developments, and handles end-to-end business management. Mr. Bralet has been with BD for 24 years, previously holding positions in the Technical Services, Marketing and R&D Departments. He earned his engineering degree at l'Institut National Polytechnique (INP) in Grenoble, France, with specializations in physical chemistry and industrial engineering.

**Megan Lan** leads Global Marketing for the safety portfolio of BD Medical-Pharmaceutical Systems. She provides commercial leadership to BD's delivery system platforms and defines, develops and launches patient-centered self-injection and safety systems, in collaboration with cross-functional, commercial and regional teams. She has also developed pen injectors and autoinjectors, and has participated in ISO committees to improve standards influencing patient safety and usability. Prior to joining BD, Ms. Lan served in public health and development with the Peace Corps in Central America, and worked in product development at Kimberly-Clark Corporation. She earned her MBA and MA at the University of Pennsylvania and has an undergraduate degree in Biomedical Engineering.



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# MANUFACTURING SOLUTIONS

## Sterile Drug Product Manufacturing During a Global Pandemic

By: Ankit Agrawal, MSc, Ronald Aungst, Jr., PhD, Jonothan Hamer, MCIPS, and Barbara Solow, PhD

### INTRODUCTION

The COVID-19 pandemic has presented public health challenges on almost every front imaginable. The scale of the public health response is unprecedented with no similarity to any other pandemic in modern times. Both privately and publicly funded researchers have applied innovation, speed, and scientific rigor to progress both therapeutics and vaccines in an unconstrained effort to halt the pandemic and save millions of lives. As biopharmaceutical companies race to find a cure or vaccine, they have become more synonymous with household brands.

At the same time, governments and not-for-profit organizations have invested heavily in vaccine and therapeutic development and delivery, while also working to adhere to the highest standards to deliver a safe and efficacious product for patients. In parallel,

FIGURE 1


**Vial Filling on Automated Line**

there have also been increased investments within countries around the world to establish long-term domestic infrastructures within countries that solidify the necessary supply chains in the event of future pandemics or other crises causing shortages of medical products.

Delivery of product to the health care front lines during the pandemic has been one of the greatest challenges facing the industry. Maintaining production requirements of existing essential medicines, in addition to expansion of the necessary capacity to supply billions of doses of vaccine to treat the global community, have accentuated the need for agility to ensure supply reliability. Manufacturers have responded to the challenges by changing how they work in numerous ways, which will keep global supply chains prepared for years to come.

## COMPOUNDING RISKS

Prior to the COVID-19 pandemic, there was already a shortage of aseptic fill/finish capacity and relevant materials. Typically, components, such as syringes, vials, and stoppers, have four- to six-month lead times. Certain essential medicines used in the treatment of COVID-19 patients have also experienced shortages due to insufficient production capacity and the need to divert the primary components toward COVID-19 products to address the pandemic.

In the context of a pandemic, it is difficult to predict which company or entity will ultimately require the necessary capacity for manufacturing at scale. The vaccine or treatment that would ultimately be successful is unknown at the start of the pandemic. CDMOs have had to take a flexible approach to assigning capacity and coordinating the procurement of material, capitalizing on disposable equipment and continuous flow manufacturing to maximize throughput and expedite delivery to patients.

When the pandemic first surged, the lack of PPE for the world's first responders was headline news. This shortage expanded beyond masks and included sterile gowning, gloves, booties, hairnets, and sleeves. One year later, PPE is rarely in the headlines, yet it remains an acute need for manufacturers as workforces have expanded and facilities are running 24/7. Demand remains high from manufacturing, health care, and other essential businesses, and nations continue to ramp up stockpiling measures.

## SOURCING AT THE FOREFRONT

Procurement organizations have played a critical role in securing the affected supply chains and have been working extensively beyond normal hours to source essential raw materials, equipment, and supplies. Procurement has often had to bypass distributors and work directly with the original manufacturers to expedite and optimize supply. A high degree of competency in sourcing has been essential to identify suppliers that can meet the technical, quality, and supply-chain requirements of the situation, as well as finding creative solutions to resolve many apparently insurmountable supply-chain obstacles.

Robust collaboration across the health care network has been vital to secure goods and services to maximize the output of finished product around the world. Government agencies in the U.S., including the Biomedical Advanced Research and Development Authority (BARDA), have stepped in to secure access and prioritize manufacturers' needs for vital equipment and materials to aid in expediting COVID-19 therapeutic and vaccine manufacture.

In most organizations, procurement quickly became recognized as a key function in the pandemic response as they worked to secure supply chains for continued operations and develop contingency plans, which could be shared across the enterprise. The plans often involved changing suppliers, finding alternative shipment routes, and where possible, qualifying secondary sources for materials and consumables.

Furthermore, the pandemic response caused supply restrictions as some countries reserved critical materials for their own domestic use. Some routinely available materials for manufacturing of pharmaceuticals were also being used in alternative production, such as alcohol in hand sanitizer, again constraining supply. For several reasons, many materials became scarce and prices rose sharply as demand outstripped supply. As time progressed through the pandemic, panic buying and political interventions have eased and additional capacities have been brought online by producers, meaning that supply chain constraints have eased to some degree.

## RAPIDLY INCREASING MANUFACTURING CAPACITY

CDMOs have worked to improve throughput time, delivering more with the same amount of facility capacity. Capital invested in facilities, optimized manufacturing processes, and maximized batch sizes have all contributed to the improvements. This has all been greatly

FIGURE 2

Vial Filling on Automated Line

accelerated during the pandemic.

Careful, yet expedited, planning is the first step toward addressing the expanded fill/finish capacity needed to manufacture the COVID-19 vaccines. Leveraging large cross-functional teams to address the planning, combined with dedicated program management of the team, is necessary to capture all requirements.

Flexibility and agility to manage numerous changes to plan is crucial as processes and needs change in real time. Last-minute changes in suppliers can result in constantly moving timelines due to various impacts across the entire supply chain, including increasing or decreasing production of upstream portions of supply and a myriad of other possibilities. Iterative versions of plans must be captured with the continuous changes caused by all of the elements that come to play in manufacturing for a pandemic.

An often-overlooked area is warehousing – a critical component that is easily underestimated during a pandemic. There is a need to stockpile when materials become available and then hold the materials until they are needed. In products that are being developed quickly, the time when the material may be needed may not be precisely known. Development delays, manufacturing delays, or at the opposite extreme, accelerated timelines have to be anticipated. A range of storage conditions and temperatures will most likely be required. There can even be the need to hold bulk drug substance prior to manufacture or product until delivery can be made to the next step in the production process. Identifying contingency storage space adjacent to the manufacturing site is key.

## TECHNOLOGY TRANSFER TO MANUFACTURING IN A FEW MONTHS

Technology transfer of commercial processes typically takes anywhere from 12 to 18 months for more complex manufacturing. The pandemic situation challenged and changed that standard. What once was routine became irrelevant. The pace at which organizations needed to operate uncovered three key areas to which focus was needed: (1) organization staffing, (2) public-private partnership, and (3) focused high-level joint management through true partnership between CDMOs and their clients.

First, skilled manufacturing personnel and labor in general has been very difficult to hire during the pandemic. The requirement to double the number of people working at a specific plant as quickly as possible is extremely challenging. There is a need to not only identify and hire people, but also train them in a highly regulated process like fill/finish, which requires aseptic techniques to ensure product quality and sterility is maintained. Deploying personnel from other sites in a company's network, even temporarily from different roles, is one quick solution. Another quick solution is compensating people to work overtime hours beyond the norm. Hiring, similar to sourcing, has required expanded and unconventional efforts. Expanding efforts within normal channels, as well as outreach into nontraditional channels and hiring as quickly as possible once candidates are identified, has been critical.

Second, keeping close ties to regional and national regulators and authorities is essential. Without well-established relationships with regulatory agencies such as the FDA and support from governmental agencies like BARDA, such velocity would not be possible. BARDA partnered with U.S.-based suppliers to expand domestic manufacturing capacity, increasing availability as part of Operation Warp Speed.

True partnered approaches, in regard to management of a tech transfer, have been quite rare in the CDMO industry. More typically, the client and CDMO work through a more transactional effort to achieve the final outcome of the tech transfer. With the pace at which pharma companies need to move into manufacturing to be ready for immediate distribution at the time of the emergency use authorization for pandemic treatments

or vaccines, transactional approaches simply are not workable. Development of a jointly owned management effort becomes more essential to ensure speed of treatments to patients while still ensuring quality and safety standards are maintained.

Expediting a technology transfer while a product is progressing through clinical development requires conducting activities in parallel that are usually conducted serially. Speed to market for emergency use authorization and immediate distribution, while maintaining rigor around quality standards, is far more critical during a pandemic than cost. In order to maintain product quality and safety as paramount, thorough risk analyses must be conducted to understand what activities could be expedited without compromising patient safety, including overlapping of clinical trial phasing, or manufacturing stockpiles of finished product prior to data on clinical success as examples.

## SUMMARY

With vaccines and treatments now available and yet more on the horizon, the first major manufacturing hurdles have been crossed. However, the finish line is still in the distance. As organizations such as drug manufacturers around the world continuously evaluate how to effectively operate, the pandemic has provided a hard reality check. Companies have seen the necessity of strong sourcing/procurement functions to enable business operations. For at least the next few years, we anticipate constraints on aseptic fill/finish and potentially API manufacturing capacity. These constraints can be mitigated by having staffing flexibility when needs arise, enabling rapid technology transfers and adding surge capacity utilization. In addition, truly partnered approaches of pharmaceutical companies and their CDMO suppliers need to be the standard for managing and operating with speed, quality, and safety rigor to meet the needs of the global impact of the pandemic and to ensure focus on the end goal. Finally, maintaining strong relationships with regulatory bodies around the world enables a strong public-private partnership both during and post pandemic, with patients as the shared motivational force to execute and deliver. ◆

## BIOGRAPHIES

**Ankit Agrawal** is the Senior Director of Global Commercial Strategy at Curia. He began his career in a clinical setting and has a 10-year history of leading corporate transformations at companies to develop and manufacture vital drugs for patients globally. He earned his MSc in Health Care Policy & Management from Carnegie Mellon University and his BSc in Biotechnology from the University of Nebraska Omaha.

**Dr. Ronald Aungst** is the Senior Director of Global Project Management at Curia and responsible for several fill/finish programs in the company's COVID-19 manufacturing efforts. He began his career at Curia working in medicinal chemistry and has expanded his breadth of knowledge into the pharmaceutical development and cGMP manufacturing platforms within the company, assuming various technical and commercial roles within the company over the past 18 years. He earned his PhD in Synthetic Organic Chemistry from Pennsylvania State University and his BA degrees in both Chemistry and Biology from Lycoming College.

**Jonothan Hamer** is Vice President of Global Procurement at Curia, where he is designing and implementing Curia's roadmap to a World Class Procurement organization. Previously, he served at Abbott Laboratories as Senior Director of Procurement. Career highlights include the discovery of Substance P as the mediator in colitis through radioimmunoassay during a study of peptide expression in visceral afferents. He was also involved in lowering the total costs of materials in the world's first AIDS drug to enable poorer countries to afford the medicine. He earned his BSc at Liverpool University in the United Kingdom.

**Dr. Barbara Solow** is Vice President of Business Development & Government Contracting at Curia. She has a 20-year history of senior leadership roles at companies to develop and manufacture products for infectious diseases, including anthrax, H5N1 and H1N1 influenza, Ebola, Zika, and most recently, COVID-19. She earned her PhD in Biochemistry from Virginia Polytechnic Institute and State University.


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| Excipient vs Strength | 375 mg telaprevir |
|---|---|
| HYPROMELLOSE ACETATE SUCCINATE 12070923 (3 MM2/S) **(Core/Content)** | 375 mg |
| SODIUM LAURYL SULPHATE (Core/Content) | 7.58 mg |
| DIBASIC CALCIUM PHOSPHATE ANHYDROUS **(Core/Content)** | 75.76 mg |
| CROSCARMELLOSE SODIUM **(Core/Content)** | 30.3 mg |
| MICROCRYSTALLINE CELLULOSE **(Core/Content)** | 75.76 mg |
| SODIUM STEARYL FUMARATE **(Core/Content)** | 29.29 mg |
| COLLOIDAL SILICON DIOXIDE **(Core/Content)** | 7.58 mg |
| POLYVINYL ALCOHOL, UNSPECIFIED **(Tablet/Capsule coat)** | 11.72 mg |
| POLYETHYLENE GLYCOL **(Tablet/Capsule coat)** | 5.92 mg |
| TALC **(Tablet/Capsule coat)** | 4.33 mg |
| FERRIC OXIDE YELLOW **(Tablet/Capsule coat)** | 0.32 mg |
| TITANIUM DIOXIDE **(Tablet/Capsule coat)** | 7 mg |
| FD&C RED NO. 40 **(Tablet/Capsule coat)** | |
| FD&C BLUE NO. 2 **(Tablet/Capsule coat)** | |

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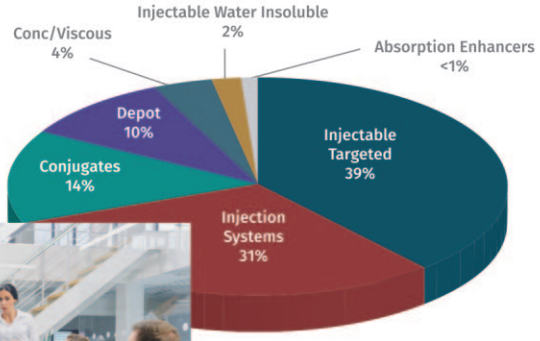


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# SYRINGE PLUNGER

# Exploring How the Functional Properties of the PremiumCoat® 1-3mL Plunger Facilitate its Implementation on Filling Lines & Enable the Delivery of Sensitive Vaccines & Biotech Drugs

By: Sebastien Cordier, Laure-Hélène Guillemot, PhD, and Audrey Chardonnet

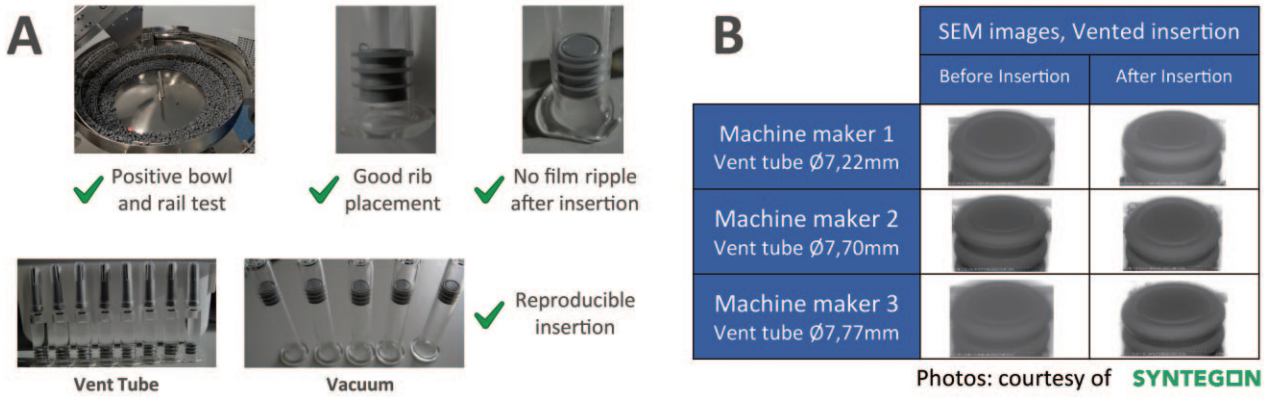
## INTRODUCTION

Whether in the development of new drug products, managing a molecule's life cycle, or when repurposing existing drugs, the choice of primary packaging is of utmost importance. It is essential that drug manufacturers understand the properties of their packaging to ensure the success of their project. The primary container, because it is in direct contact with the drug product, plays a central role in ensuring the drug is protected over time, from filling through to short- or long-term storage, and to the point of administration to the patient. Primary container failure may compromise the drug's integrity, which, aside from financial implications for the drug manufacturer, can seriously put patients at risk.

To fight Covid-19, the industry developed highly-sensitive vaccine technologies and turned to coated elastomeric closure components to minimize development risk, which put an unusual strain on global availability and led to a significant increase in lead-time for these components. As the fight against the global pandemic persists and vaccination campaigns continue to be rolled-out, the emergence of new Covid-19 variants suggests that, once under control, this pandemic could become a seasonal epidemic. Drawing from our experience with the flu, we know seasonal vaccination is very different from the mass-vaccination context we are currently experiencing. Instead of relying on large vaccination centers, where many vaccinations are performed sequentially, seasonal vaccines are usually administered by trained nurses, physicians, or even pharmacists, directly from their respective healthcare settings. In this context, single-dose Pre-Filled Syringes (PFS) become highly relevant, as they limit drug waste compared to multi-dose vials, and significantly simplify the administration process. Furthermore, pharma companies and contract manufacturing organizations are looking to strengthen their supply chains to ensure they can sustain spikes in demand or avoid exclusive dependency on suppliers. As such, the validation of a second source of supply is an ideal strategy to de-risk operations and ensure long-term security of supply.

Aptar Pharma has leveraged 50 years of expertise in the development and manufacturing of PFS components to further add to the PremiumCoat® platform with the introduction of the 1-3mL syringe plunger format. Building on the success of PremiumCoat 1mL long film-coated stopper's technology and partnership with BD, the PremiumCoat 1-3mL syringe plunger combines a pure Bromobutyl formulation with a market-proven Ethylene tetrafluoroethylene (ETFE) film that acts as a barrier to limit the transfer of rubber leachables into the drug product. The 1-3mL plunger addresses the needs of sensitive vaccines, large-volume biologics, and facilitates vial-to-prefill projects. Aptar Pharma performed a series of tests to demonstrate how the PremiumCoat 1-3mL sy-

## FIGURE 1




**Machinability testing with steam-sterilized PremiumCoat® 1-3mL plungers.**
**A) The plungers were tested on standard vacuum or vented filling lines. Their performance was evaluated in bowls and rails. The placement of the plunger, film integrity, and reproducibility of insertion were visually inspected.**
**B) The integrity of the ETFE film was controlled by Surface Electron Microscopy (SEM) before and after vented plunger insertions, using three different machines with different vent tube diameters. Photos courtesy of Syntegon.**

ringe plunger operates on different filling lines and how its properties may facilitate manual injection and auto-injector integration, while preserving the drug's integrity.

## PREMIUMCOAT® 1-3ML CAN BE HANDLED BY BOTH VENTED & VACUUM STOPPERING MACHINES

Once the drug is filled in the PFS, the plunger is inserted to seal the device via one of the two main methods frequently used on the market. The first is referred to as vented placement and relies on the insertion of a hollow tube inside the PFS called the vent tube. The plunger is placed on an insertion rod, forced through the vent tube, and exits on the other side to expand into the PFS, with the air being vented out around the stopper to avoid pressure building up. Though this method is preferred on high-speed filling lines for its rapidity and relatively easy implementation, it generates a bubble in the syringe, which may lead to further issues, for example, when transporting the filled syringe in a depressed environment such as a cargo plane. Furthermore, because the plunger is forced through a tube with a smaller diameter than that of the syringe, it induces a significant deformation of the elastomer. This may be particularly critical in the case of film-coated plungers and may impair the film's integrity, as observed with other ETFE-coated stoppers, which may negatively affect the drug-plunger compatibility.[1]

The second plunger placement method is the vacuum placement. It relies on the creation of a vacuum in the filling environment and positioning of the plunger at the top of the syringe. Upon restoration of atmospheric pressure, the differential pressure pulls the plunger inside the syringe barrel. This method significantly limits the size of the bubble and does not deform the plunger, thus preserving the integrity of the film coating. However, this method is usually slower than vented placement.

Aptar Pharma's PremiumCoat 1-3mL ETFE film-coated plunger was tested with both vacuum and vent-tube stoppering machines from various manufacturers. With the latter, the integrity of the ETFE film was controlled by camera inspection before and after insertion.

PremiumCoat 1-3mL was found to perform well in the bowls and rails. The plungers did not stick to each other and were efficiently oriented before being fed into the rails, through which the plungers travelled easily. Testing of the vacuum and vented placements showed consistently good placement of the ribs, which were well positioned, and the film was found to be unaltered (Figure 1A). In the case of vented insertion, which is known for altering ETFE-films in other coated plungers, the surface electron micrographs show that, regardless of the vent-tube diameter, the film remains intact after insertion (Figure 1B).

These data confirm that, at this stage of development, PremiumCoat 1-3mL

plungers are compatible with both vacuum and vent-tube technologies, facilitating the implementation of PremiumCoat on customer filling lines. The demonstrated compatibility with vented placement unlocks new opportunities for vaccine manufacturers working with high-speed vent-tube filling lines who wish to secure their drug development with ETFE film-coated plungers.

## PREMIUMCOAT® 1-3ML PLUNGERS MAINTAIN CONTAINER CLOSURE INTEGRITY DURING TRANSPORT

Syringes stoppered using the vented method can include a bubble that is in contact with the plunger. When PFS are then transported by plane, they may be xposed to a significant reduction in atmospheric pressure within cargo environments. Because of the pressure difference and the presence of a bubble, the plunger is likely to move outward. Even though PFS are packaged in aseptic conditions, only the inside of the PFS is guaranteed to be sterile, and a significant outward movement of the plunger may expose the drug to a section of the glass where sterility is not ensured.

To investigate this possibility, Aptar Pharma performed a test in which the syringes filled with a solution also included a bubble of defined size. The PFS were exposed to a depression of equivalent magnitude to a cargo flight, and the movement of the plunger was measured. The container sterility is considered compromised if a plunger moves more than twice the inter-rib distance. Because the plunger is composed of three ribs, a movement of two inter-rib would place the rib on the drug side at the position of the rib initially on the outside, therefore exposing it to the external environment.

While vacuum plunger placement minimizes the size of the headspace bubbles (typically below 1 mm), vented placement can generate bubbles of up to 6 mm in a worst-case scenario. Figure 2B shows that, even with a 6 mm headspace, the PremiumCoat 1-3mL plunger's movement remains largely below the reject criteria, and the plunger moves by less than one inter-rib distance.

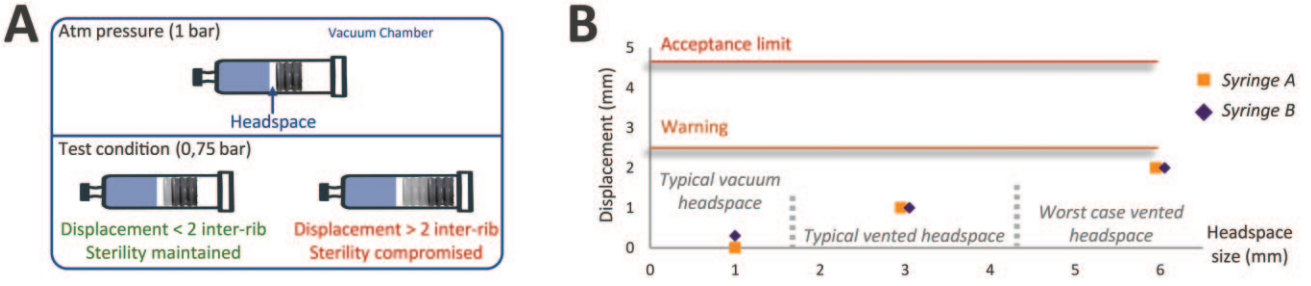
These results indicate that, under the conditions of these tests, the PremiumCoat 1-3mL plunger ensures the drug remains sterile during air freight, even if a sub-optimal vented placement was operated.

## PREMIUMCOAT® 1-3ML PLUNGER FACILITATES INJECTIONS & AUTO-INJECTOR INTEGRATION

The break-loose force describes the strength required to initiate the movement of the plunger in the barrel, while the gliding force designates the strength needed to continue this movement. These parameters are essential to a successful injection, as they are directly related to the ease-of-use of a PFS and define whether the PFS could be integrated in an auto-injector to facilitate further improvement in the injection process.

When the plunger is inserted into the syringe barrel, it may be stored for a prolonged period, during which the rubber is in contact with the glass. Because the plunger must maintain container closure integrity, its diameter is designed to be slightly higher than that of the barrel to maintain a degree of compression and ensure container closure integrity. In order to

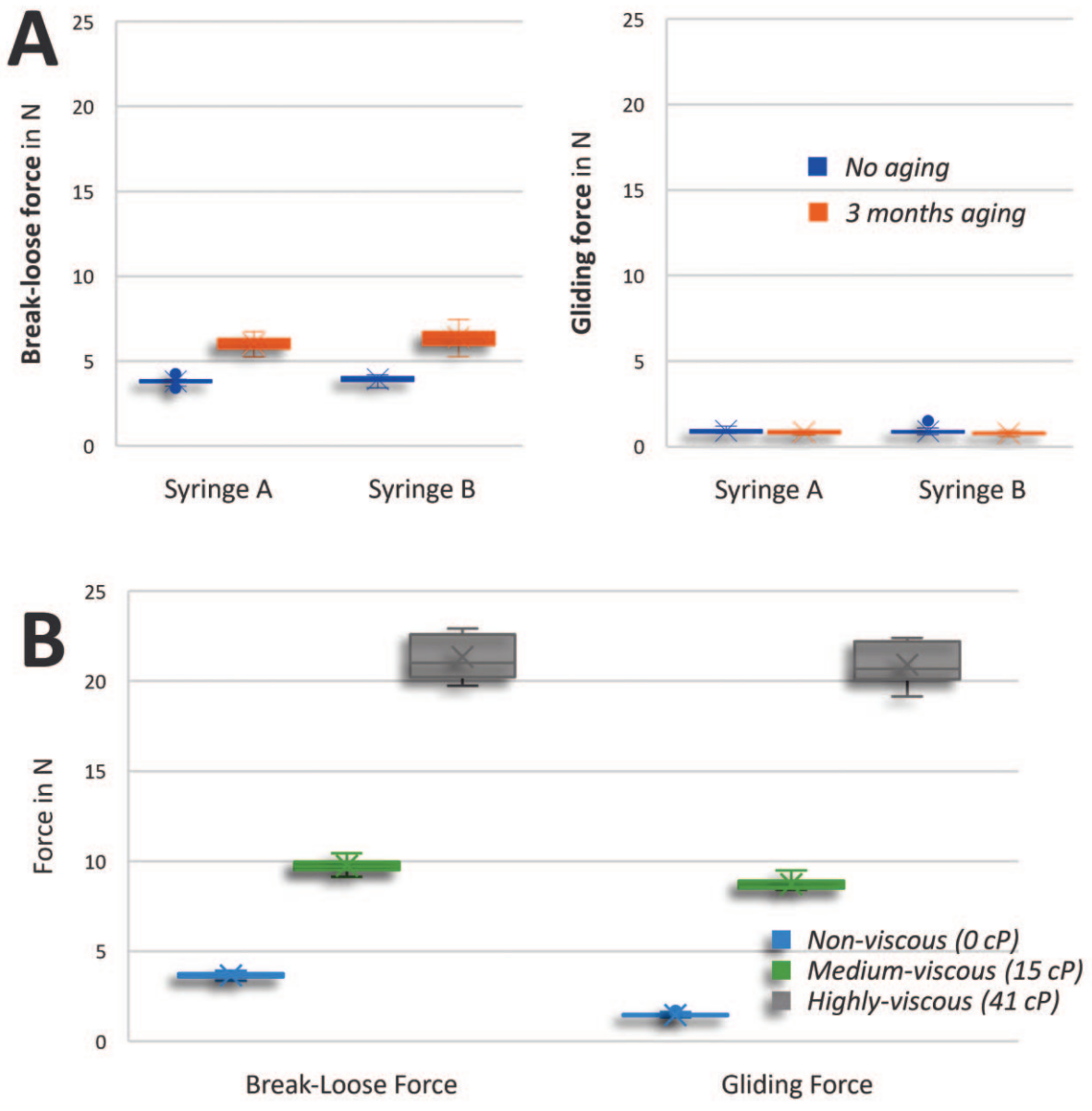
**FIGURE 2**




**Transport test with steam-sterilized PremiumCoat® 1-3mL plungers.**
**A) Representation of the experimental setup. The syringes were stoppered at atmospheric pressure with a given bubble size (headspace size), placed in a vacuum chamber at a pressure of 750 mbar before and the atmospheric pressure subsequently restored.**
**B) The plunger's movement is measured for each head space size. The reject criteria were defined as a displacement equal to two inter-rib distances.**

"Aptar Pharma has leveraged 50 years of expertise in the development and manufacturing of PFS components to further add to the PremiumCoat® platform with the introduction of the 1-3mL syringe plunger format. Building on the success of PremiumCoat 1mL long film-coated stopper's technology and partnership with BD, the PremiumCoat 1-3mL syringe plunger combines a pure Bromobutyl formulation with a market-proven Ethylene tetrafluoroethylene (ETFE) film that acts as a barrier to limit the transfer of rubber leachables into the drug product."

**FIGURE 3**




**Functional testing of steam-sterilized PremiumCoat® 1-3mL plungers in 2.25mL syringes.**
**A) Break-loose forces and gliding forces measured in empty syringes at 300 mm/min, with steam-sterilized plungers without aging and after 3 months aging at 40°C.**
**B) The break-loose and gliding forces were measured at 100 mm/min in syringes filled with various fluid viscosities and with stoppers that have not been aged.**

facilitate the movement of the plunger inside the barrel, both the glass and the rubber are lubricated with silicon oil. The break-loose and gliding forces therefore depend directly on the siliconization process and the design of the plunger. These values help facilitate the manual injection process, with lower forces usually associated with a perceived ease of injection. On the other hand, variability of break-loose and gliding forces between products is essential in enabling auto-injector integration. These secondary devices use mechanical springs whose force is carefully controlled; a weak spring would not enable the delivery of the drug under an appropriate time, while a spring that is too strong may be associated with painful injections.

With the increased use of biologics, and ongoing efforts to improve adherence and comfort of injections in the context of chronic disease treatment, pharma manufacturers are looking to reduce the number of doses that patients need to receive via injection. This is typically done by increasing both the volume of the injection and the concentration of the drug, with the latter leading to an increase in the viscosity of the solution. Therefore, injection devices must ensure that the delivery of such solutions can be performed as expected, with or without an auto-injector. This again depends on the functional performance of the elastomeric plunger in conjunction with the syringe.

Aptar Pharma's technical experts assessed the break-loose and gliding forces of PremiumCoat 1-3mL plungers when inserted into different syringe barrels and with fluids of various viscosities. These forces were measured using a dynamometer as the plunger travelled through the barrel at constant speed. Each measurement yields a graph of forces which is analysed to extract the break-loose force and average gliding forces.

When comparing syringes from two different suppliers, Aptar Pharma's PremiumCoat demonstrated consistent break-loose and gliding performance (Figure 3A). For a given syringe, aging was observed to lead to a mild increase of the break-loose force (less than 3N) but no increase of the gliding force. In all cases, over the 15 replicates, the results show very little variability, indicating consistent performance across plungers.

When simulating an injection with solutions of various viscosity, we observed a gradual increase of both the break-loose and gliding force (Figure 3A). This increase was expected according to Poiseuille's law, which states that the force in such a system is directly proportional to the viscosity of the fluid. It is interesting to note that the difference between the break-loose and gliding force remains similar for each condition. This indicates that the solution's viscosity does not significantly affect the performance of the PremiumCoat plunger, and the forces remain under 25 N.

Taken together, these results demonstrate that the Aptar Pharma PremiumCoat 1-3mL plunger performs consistently well in biotech syringes, enabling the delivery of high-viscosity drugs. The low break-loose and gliding forces are compatible with manual injection, and remain within a patient's abilities, even for those suffering from rheumatoid arthritis who can deliver average forces of at least 30 N.[2] The low variability within the sample and high consistency between break-loose and gliding force indicate that PremiumCoat 1-3mL would facilitate integration into an auto-injector.

## APTAR PHARMA'S PREMIUMCOAT® 1-3ML-PLUNGER FULFILLS KEY DRUG DELIVERY REQUIREMENTS FOR VACCINE & BIOTECH APPLICATIONS

At this stage of Aptar Pharma's PremiumCoat 1-3mL plungers development, the series of validation testing performed on the product show promising results and demonstrate that the product meets key requirements for addressing sensitive vaccines and biotech drugs:

- **PremiumCoat performed well on vacuum filling lines and, in contrast with other film-coated plungers, can be processed by vent-tube technology without altering the film's integrity.[1] Aptar Pharma's plunger can therefore be easily integrated on common filling lines, including high-speed filling lines that use vented placement.**
- **When using air freight, and even in the case of a large headspace, PremiumCoat plunger movements remain controlled and do not jeopardize the drug's integrity.**
- **PremiumCoat 1-3mL plungers perform well in glass syringes, and the force required to perform an injection remains largely within a patient's capabilities. The consistency of the break-loose and gliding forces across situations and aging may facilitate the integration into auto-injectors.** ◆

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## BIOGRAPHIES

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

**Dr. Laure-Hélène Guillemot** is Project Leader within Aptar Pharma's Injectables division. An engineering graduate of the Superior School of Chemistry Physics and Electronics, Lyon, France, she also earned her PhD in Chemical Physics from CEA-Leti, Grenoble, France. Having worked over 6 years in the construction products industry, she developed a strong expertise in glass chemistry and project management for product development. She joined Aptar Pharma in 2020 and in her current role is involved with new product development, including Aptar Pharma's PremiumCoat® solutions.

**Audrey Chardonnet** is the Global Business Development Director for Prefillable Syringe Components (PFS) at Aptar Pharma's Injectables division and is responsible for driving overall strategy for PFS segments. She previously held several positions within the Aptar Pharma sales organization, most recently as Director, Global Strategic Customers, with a particular focus on business development with syringe manufacturers. She graduated with an Engineering Master's Degree in Chemistry and has over 12 years of experience in the injectables industry.

Drug Development
EXECUTIVE

Catherine Hanley

VP & Interim CDMO Business Unit Head

Emergent BioSolutions

emergent CDMO

# Emergent CDMO: Making the Impossible, Possible for Biopharma Innovators

The path from biotherapeutic or vaccine concept to market is a demanding one that requires a combination of resources, experience, capacity, and commitment. Engaging with the right contract development and manufacturing organization (CDMO) partner at the right time can get you from where you are to where you want to be. Having an experienced and knowledgeable team by your side can make all the difference, especially when navigating the complexities of drug development and manufacturing.

Emergent BioSolutions' mission is to protect and enhance life through innovation. Throughout the past few decades, Emergent has developed, manufactured, and delivered therapeutics and vaccines throughout the world to tackle the most serious health threats. Emergent's CDMO business draws on this experience to have supported the development and manufacture of over 40 commercial and more than 200 clinical programs for their clients. As a dedicated and supportive CDMO solutions partner, clients can leverage Emergent CDMO's diverse technology platforms, customizable solutions, and experience to support the clinical and commercial successes of their molecules.

*Drug Development & Delivery* recently interviewed Catherine Hanley, Vice President & Interim CDMO Business Unit Head at Emergent BioSolutions, to discuss the company's plans for current and future CDMO operations and client partnership opportunities.

**Q: Emergent CDMO is an embedded business unit within Emergent and has been growing steadily over the past few years. What was the motivation behind leveraging Emergent's development and manufacturing capabilities externally?**

**A:** We recognized a unique opportunity to partner with some of the biggest innovators in biopharma to support bringing their molecules to market. We have a long history of developing and bringing therapeutics and vaccines to market, so it was a natural fit to grow into a service provider, sharing this experience and applying our expertise throughout the drug development lifecycle from development services to drug substance and drug product manufacturing.

Our knowledge and technical expertise in working with numerous diverse and complex molecules allows us an opportunity to provide individualized and integrated offerings and tailored approaches for a variety of products. Our unique value lies in the flexibility of our capacities, capabilities, and scalable offerings for a broad range of technology platforms. Clients work with us to meet their product goals and aggressive timelines from early phase to commercialization.

**Q: What differentiates Emergent CDMO from its competitors?**

**A:** Emergent has a strong foundation of technical expertise working on complex science. We have a strong track record for developing, manufacturing, and delivering our own innovative vaccines and biotherapeutic products to combat public health threats and infectious diseases, which relies on dynamic solutions like speed, flexibility, and innovation. We understand first-hand what it takes to bring a drug from development through to commercialization, and there's no substitute for that experience.

Our CDMO business leverages the talent, capabilities, and expertise from across the organization to support the development and manufacturing needs of our biopharmaceutical customers. Across the company, in addition to a tremendous team of manufacturing science and technology experts, our technical and compliance professionals have extensive experience, and stand ready to support our customers though the challenges of scaling-up and manufacturing their clinical and commercial programs.

We are not simply an embedded CDMO, but instead we are an integrated CDMO, built on Emergent's existing foundation. We have the knowledge to help our clients anticipate what's coming next, the infrastructure and processes to help adapt, and the expertise to provide the kind of insights that can help avert unnecessary and costly delays. This positions us to be able to focus directly on our clients and their successes, and to be ready for changing needs.

**Q: How are you applying those strengths as a development and manufacturing partner?**

**A:** Our development and manufacturing facilities in North America and Europe are strategically located in close proximity to our pharmaceutical and biotechnology customers. Each site provides its own unique set of strengths and experience, allowing us to meet our clients' diverse drug program needs.

Our Center of Excellence for Development Services is located in Gaithersburg, MD. The Development Services team specializes in formulation, process, and analytical method development, including Biosafety Level 2 (BSL2) capabilities for both drug substance and drug product development and scale-up needs.

With locations in the US, Canada, and Switzerland, our five drug substance facilities specialize in our differing technology platforms, providing innovative, flexible, and customizable biotherapeutics and vaccine manufacturing, including single use and disposable technologies.

Our three North American drug product manufacturing facilities provide the manufacturing capacity, equipment flexibility, including lyophilization, isolation technologies and terminal sterilization, visual inspection capabilities, and packaging and labeling services to provide aseptic fill/finish services for our clients' drug product from clinical programs through to commercialization.

**Q: How are Emergent's current technologies and platforms influencing your business strategy?**

**A:** Our development and manufacturing teams have extensive experience and expertise to support our client's needs for a wide range of platforms and technologies, including mammalian, microbial, viral, and plasma protein-based biotherapeutics and vaccines. Recently, we began providing process and viral vector development services for gene therapies.

We offer a complete range of process development capabilities from early testing quantities to developing robust,

scalable, and transferable processes for cGMP drug substance and drug product manufacturing. Our analytical team customizes phase-appropriate testing to the required needs of our clients' molecules, providing comprehensive understanding and characterization during each milestone of development and commercialization.

Additionally, our drug substance facilities house the capacity and capabilities in cGMP upstream and downstream manufacturing, including the use of single-use bioreactors (SUBs) and fermenters and a state-of-the-art BSL3 manufacturing suite, allowing us to meet our client's needs as they evolve, from clinical development to commercialization.

We offer a comprehensive range of drug product formulation and aseptic filling in vials and pre-filled syringes in various configurations to address both viral and non-viral manufacturing needs from early-stage clinical products to late-stage commercial products. We also offer cGMP lyophilization in conjunction with our fill/finish capabilities.

We pride ourselves on being a truly integrated CDMO, and by providing customizable service offerings, capabilities, capacity, along with our experience and expertise, we are able to offer molecule-to-market biologics development and manufacturing services, with a specific focus on our clients and their successes.

**Q: Is there anything that Emergent CDMO is doing to streamline tech transfer activities for clients' products or processes?**

**A:** Earlier this year, we introduced our rapid start and scale manufacturing program, which helps our clients reach their next milestone quickly, without sacrificing quality or reliability. In 90 days, we can go from project inception to manufacturing by providing seamless tech transfer and an experienced and dedicated project management team.

With this program, projects are successfully onboarded and a client's first GMP fill can be completed in 90 days, supporting even the most rigorous timelines. Our experienced teams from analytical and tech transfer to project management, manufacturing, supply chain, and procurement work in tandem to expedite manufacturing timelines by finding solutions to challenges and reducing manufacturing variables. Recently, for a client using our 90-day rapid start and scale, we were able to complete a tech transfer in record time – putting their project ahead of schedule.

**Q: Looking ahead, what growth opportunities is Emergent CDMO pursuing for 2022 and beyond?**

**A:** In 2020, Emergent announced a $75-million investment into its Canton, MA, drug substance facility to increase the campus footprint and expand its manufacturing capabilities into viral vector-based gene therapy. This investment will include a state-of-the-art, multi-suite with manufacturing capacity up to 1000 L in scale. The expansion bolsters our integrated CDMO service offering for development and manufacturing of viral vector-based gene therapies.

In addition, we've also been significantly enhancing our drug product aseptic fill/finish capacity and capabilities at several sites. This year, our Camden facility (drug product manufacturing site in Baltimore, MD) began manufacturing operations with a new state-of-the-art Groninger® FlexPro 50. The FlexPro 50 utilizes isolator-based technology for aseptic processing of pre-sterilized syringes, cartridges, and vials and can support liquid or lyophilized products.

Our viral drug product facility in Rockville, MD, is currently undergoing a 58,000-sq-ft expansion that will include a state-of-the-art high-speed fill/finish line with fully integrated isolator technology and an automated inspection, labeling and packaging line, enhancing our capabilities in large scale fill/finish manufacturing of viral biotherapeutics and vaccines.

Finally, our development and manufacturing site in Winnipeg, Manitoba, Canada, houses a state-of-the-art Vanrx® SA25 Aseptic Filling Workcell, providing clients with a high level of sterility assurance through an automated handling, filling, and closing process, designed to minimize line losses. ◆

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# DRUG DELIVERY

## CAPRO™: A New Advance in Polymeric Drug Delivery

By: Bob Wieden and Chun Wang, PhD


### ABSTRACT

The estimated global market size of drug delivery products was $1.4 trillion in 2020. Unfortunately, 40% of marketed drugs and 90% of pipeline drugs (mostly small molecules) are poorly soluble in water, which makes parenteral, topical, and oral delivery difficult or impossible. In relation, poor solubility often leads to low drug efficacy. Add in the fact that many other hurdles exist in the form of drug loading, stability, controlled release, toxicity, and absorption – it's not hard to understand the difficulties in bringing new drug products to market. Additionally, biopharmaceuticals (proteins, peptides, nucleic acids, etc) and combination drug products possess many of these same problematic obstacles that affect efficacy. These challenges, coupled with the complexity and diversity of new pharmaceuticals, have fueled the development of a novel polymeric drug delivery platform called CAPRO™ that overcomes a great many bioavailability and delivery obstacles. By leveraging TREKKA Therapeutics proprietary CAPRO polymer platform, pharmaceutical and biopharmaceutical companies can improve dosing accuracy, efficacy, and reproducibility in their drug discovery and drug delivery research. In summary, the CAPRO platform is designed to lower costs, reduce side effects, improve patient compliance, and expand drug access though improved administration methods.


### CHALLENGES IN COMPOUNDS & IN DRUG DISCOVERY

The demand for pharmaceutical products worldwide is only going to increase in the coming years, as old and emerging diseases continue to threaten the well-being of people globally. Drug discovery efforts are expected to intensify, generating a large variety of active compounds with vastly different structures and properties. However, it is well known that despite tremendous output of the drug discovery process, the success rate of a candidate compound becoming an approved drug product is extremely low. The majority of candidate compounds are discarded due to various hurdles in formulation and preclinical testing (such as issues with solubility, stability, manufacturing, storage, and bioavailability) before even entering into clinical studies. Therefore, advances in formulation and drug delivery, especially the development of new and versatile biomaterial platforms as effective excipients, may salvage many "difficult," otherwise triaged, drug compounds, and significantly enhance their chance of becoming viable drug products. Furthermore, breakthroughs in biomaterial platform technologies will also facilitate life cycle management of existing APIs through reformulation, repurposing of existing APIs for new indications, and development of combination products consisting of multiple APIs.

## CHALLENGES FACING SMALL-MOLECULE DRUGS

Small-molecule drugs are typically classified by the Biopharmaceutical Classification System (BCS) in terms of their solubility and permeability through biological tissue barriers.[1] Of particular challenge are the BCS classes II and IV: both suffer from low aqueous solubility. In fact, 40% of marketed drugs and 90% of pipeline drugs are poorly soluble in water.[2] BCS class IV compounds further suffer from low tissue permeability. The absorption of oral drugs takes place in the small intestine, and low solubility limits the maximum drug concentration that can be absorbed. In most cases, slow diffusion is almost always associated with low solubility but can be compounded by small drug surface area and/or slow diffusion rates in the gastrointestinal (GI) tract. The common problem is that a slow diffusion rate may limit drug absorption, particularly when the solubility of the drug product is so low that the drug concentration must be preserved near its maximum solubility limit so that enough drug can be absorbed during the limited time the drug transits the GI tract. Further, the propensity of many drugs to crystallize is another hurdle that makes drug solubilization and absorption difficult.

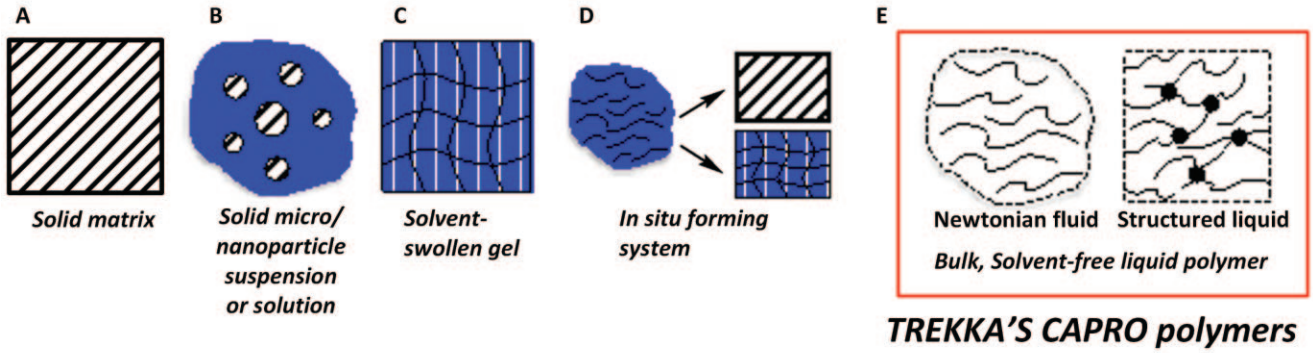
Current formulation strategies to enhance drug solubility include solubility enhancers (such as cyclodextrin, lipids, surfactants), drug micronization, salt formation, and amorphous solid dispersion in polymeric excipients for oral delivery.[3] Organic solvents, though undesirable, are used in some injectables.[4] However, these approaches have a number of weaknesses. They are not particularly effective toward highly insoluble drugs and not easily adaptable to achieve various drug-release kinetic profiles. Some formulation processes are complex and require specialized equipment. APIs and excipients may be damaged during melting and extrusion under high temperature. Certain excipients and solvents can be toxic or cause allergic reaction in some patients. Degradation of common polymer excipient families, such as poly(lactide-co-glycolide) (PLGA), produces harmful acidic by-products, causing inflammation.[5] PLGA undergoes bulk degradation *in vivo* by hydrolysis of the ester linkages within the polymer backbone. The reduction of polymer molecular weight and erosion of the polymer measured by mass loss are inconsistent, thus, like other bulk-degrading polymers, it is difficult to control the release kinetics of drugs, especially at high drug loadings. Infiltration of water into the PLGA matrix can also compromise the stability of the drugs during storage and long-term *in vivo* residence.

## CHALLENGES FACING BIOPHARMACEUTICALS

Unlike small-molecule drugs, biopharmaceuticals, including peptides, proteins, nucleic acids (DNA, RNA), are large molecules that present unique challenges.[6] A major concern is loss of molecular stability and bioactivity due to degradation by hydrolysis, oxidation, and enzymatic reactions and denaturation due to heat, pH, and organic solvents, resulting in short shelf-life and *in vivo* half-life. Also, large molecular size and surface charges make it difficult for these biomacromolecules to diffuse across tissue and cellular barriers. Additionally, many peptides and proteins are prone to aggregation at high concentrations, limiting the loading and bioavailability of these drugs.

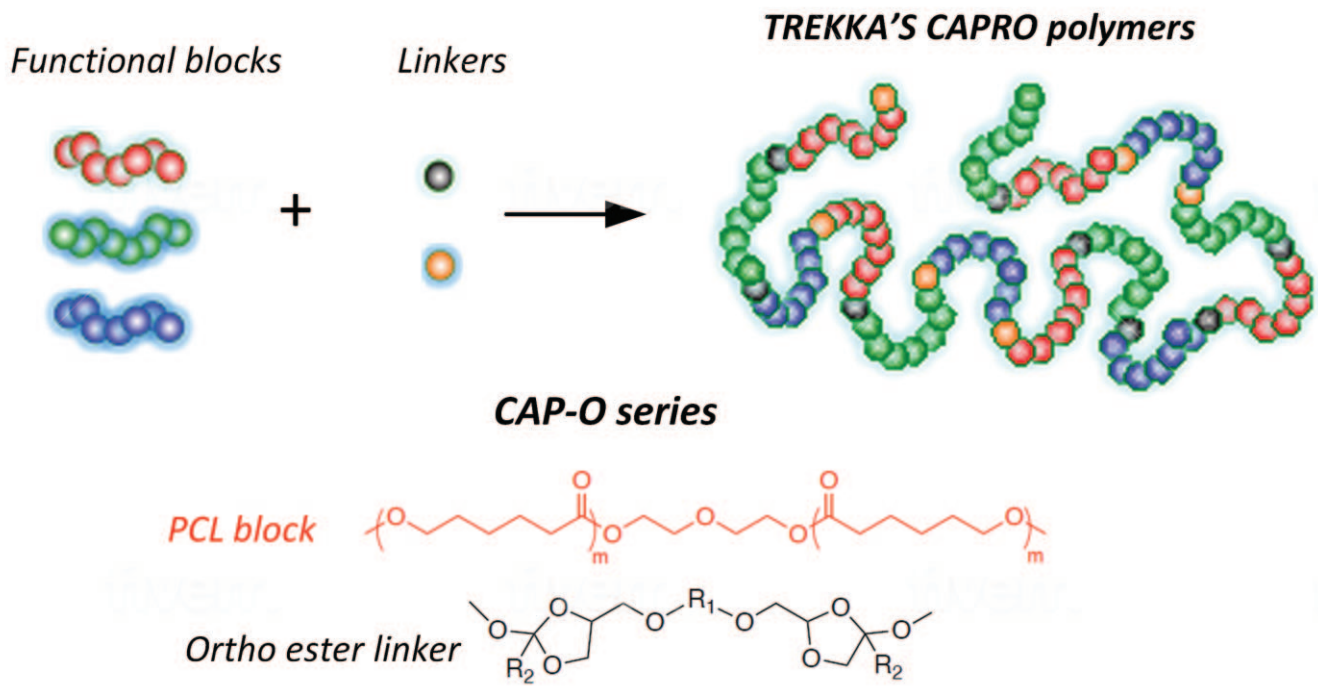
Bulk-degrading polymers, such as PLGA, are widely used for the controlled release of biological macromolecules, especially peptides and proteins.[5] Because most peptides and proteins are hydrophilic, the loading efficiency of these molecules in hydrophobic PLGA is often

**FIGURE 1**




**CAPRO polymers exist as either Newtonian fluids or structured liquids at physiological temperature, unlike conventional polymeric biomaterials.**

FIGURE 2



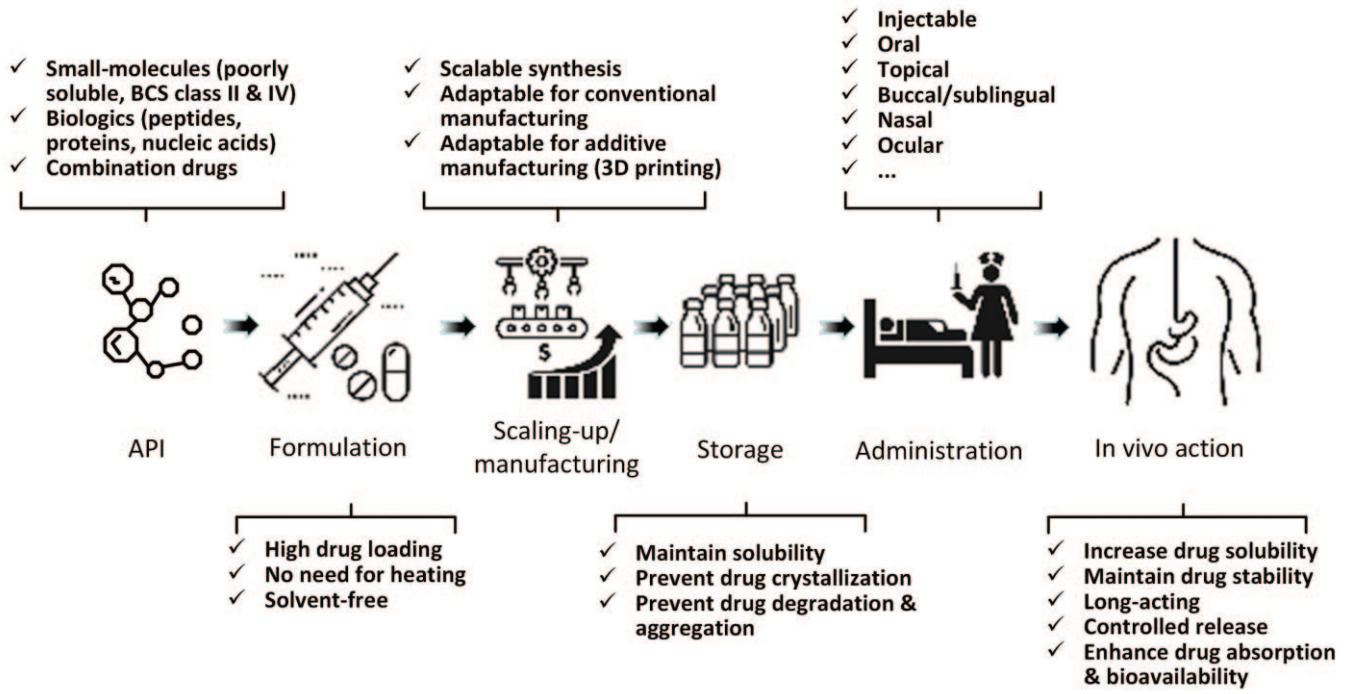

**Modular design of CAPRO polymers by combination of a variety of functional blocks with specially designed linkers. An example is the CAP-O series of polymers consisting of PCL functional block and ortho-ester-containing linkers.**

quite low. The preparation of PLGA formulations requires organic solvents at elevated temperatures and may cause protein denaturation or aggregation. Residual solvent in the drug product can be toxic to the human body. Accumulation of PLGA degradation products results in an acidic environment that can damage and deactivate delicate biopharmaceuticals. Also, the drug release rate is difficult to control, due to the random nature of PLGA degradation and bulk erosion. Hydrophilic polymers, such as polyethylene glycol (PEG), have also been used to facilitate peptide and protein delivery. PEGylation, the conjugation of PEG to peptide and protein drugs, offers protection against enzymatic degradation, aggregation, and non-specific capture and clearance by the reticular-endothelial system (RES).[7] PEGylated drugs show longer *in vivo* half-life and blood circulation time than non-PEGylated forms. However, PEGylation requires complicated and laborious chemical reactions and can be difficult to scale up. Further, hydrogels have been used to encapsulate biopharmaceuticals and provide sustained release; however, the aqueous environment of hydrogels does not protect the cargos from hydrolytic degradation. The release of peptides and proteins from hydrogels usually lasts for days, rather than weeks or months.

## CHALLENGES FACING COMBINATION DRUGS

Drug products containing multiple APIs formulated using the same biomaterial excipients present unique challenges in formulations and delivery.[8] APIs may have different molecular size, solubility, miscibility, crystallinity, stability, and reactivity. Combining them in the same dosage form and accommodating the disparate needs for solubilization, stabilization, and release profiles will require careful selection of sophisticated solvents and excipients. APIs in combination drugs may act through different synergistic mechanisms to treat diseases. They may have different therapeutic windows (eg, effective and toxic dosing thresholds), different pharmacokinetic profiles (eg, zero order versus first order versus burst release), different duration of release, and different therapeutic targets at the organ, tissue, and cellular levels. The ideal drug delivery system for combination drugs should be able to package multiple APIs together at high doses, maintain their stability, and modulate their spatiotemporal release to reach therapeutic targets.

## FIGURE 3




**The CAPRO polymer platform addresses a multitude of challenges in drug development.**

## THE CAPRO POLYMER PLATFORM

TREKKA's CAPRO polymers provide a flexible and versatile biomaterial platform to address major challenges in drug formulation and delivery. Biodegradable polymers for drug delivery assume a few common physical forms (Figure 1). Hydrophobic polymers, such as PLGA, can form implantable solid matrices or injectable micro/nanoparticles.[9] Hydrophilic polymers, such as PEG, can be cross-linked into solvent-saturated gels (hydrogels). In situ forming systems refer to a liquid precursor turning into a solid matrix or gel after injection into the body.[10] Such phase transformation is often achieved through molecular assembly or precipitation driven by changes in solvent, temperature, or chemical reactivity. In contrast to these current materials, the CAPRO platform is based on bulk solvent-free polymers in the liquid state (liquid polymers) (Figure 1) – a unique physical state of materials with interesting properties for applications in biomedicine and particularly in drug delivery.

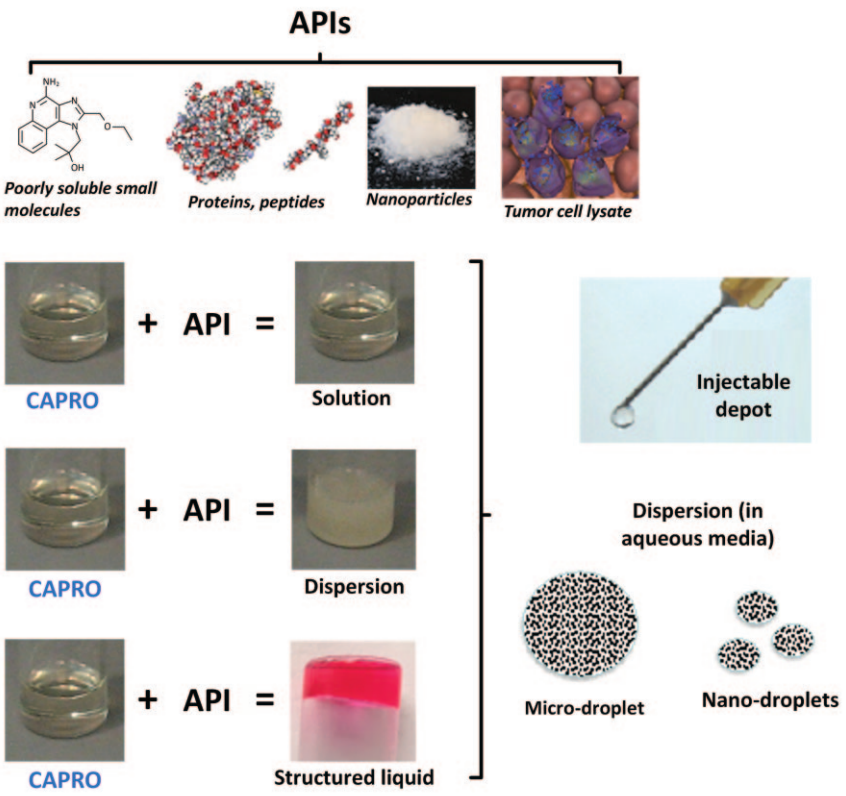
At the molecular level, a typical liquid polymer consists of disentangled chains that are flexible and amorphous with low glass transition ($T_g$) and melting temperatures ($T_m$).[11] These will ensure that such polymers behave as viscous, Newtonian fluids at room and physiological temperatures. In some cases, disentangled chains of a liquid polymer can be "structured," forming a solid-like composite with unique rheological properties.[12]

Only a handful of synthetic liquid polymers have been reported to date for drug delivery applications. Known as "thermoplastic pastes" or "semi-solid polymers," these materials include poly-orthoesters, alkyl polyesters, star PLA-castor oil, and polycarbonates.[11,13] Chemical synthesis of such polymers often requires complicated processes that are difficult to scale up. The biodegradation process of polyester-based materials lacks control, and in some cases, leads to the accumulation of acidic by-products. Furthermore, none of these polymers is capable of forming "structured" liquids. The CAPRO polymer platform overcomes these deficiencies and allows for full exploitation of the liquid polymers to address the challenges in drug delivery.

## MOLECULAR DESIGN PRINCIPLES OF CAPRO[14,15]

CAPRO polymers are designed specifically to overcome many of the weaknesses of current polymers for drug delivery. The CAPRO polymers share a generic molecular structure consisting of functional blocks and degradable linkers (Figure 2). The highly modular nature of such design makes it possible to generate a large array of polymers with diverse functionalities. The molecular features of the CAPRO polymers can be engineered to create specific interactions with specific

## FIGURE 4




**A wide range of APIs has been incorporated into the CAPRO polymers. These include poorly water-soluble small molecules such as resiquimod (an immunostimulatory adjuvant) and paclitaxel (an anticancer drug), which can be dissolved directly into solvent-free CAPRO at high concentrations. Various peptides and proteins (such as ovalbumin and albumin) have been loaded into CAPRO to form particulate dispersions. Nanoparticles such as silica have been found to form structured liquids with some CAPRO compositions. Finally, total tumor cell lysate has been loaded into CAPRO and tested as a potential cancer vaccine.**

APIs in ways that promote drug dissolution and loading, preserve drug stability during storage, and achieve controlled drug release, leading to improved bioavailability and efficacy.

One class of CAPRO polymers is the CAP-O series (Figure 2). Here, polycaprolactone (PCL) is chosen as the primary functional block for its excellent biocompatibility and low $T_g$ and $T_m$.[16] The linker may contain labile chemical bonds, such as the ortho ester bond, which can determine the kinetics of polymer degradation and in turn, dictate the rate of drug release.[17] The length and number of the PCL block (and other potential functional blocks) as well as the chemical structure of the linker can be manipulated independently depending on the need of specific drugs, route of administration, and desirable pharmacological profiles.

## ADVANTAGES OF CAPRO POLYMERS IN ACCELERATING DRUG DEVELOPMENT[14,15]

The CAPRO polymer platform is developed to provide solutions to multiple challenges and hurdles in drug formulation, manufacturing, storage, administration into patients, and *in vivo* pharmacological action (Figure 3).

### APIs

CAPRO polymers are compatible with both small-molecule and large-molecule APIs as well as combination drugs (Figure 4). For poorly soluble small molecules, the CAPRO polymers serve as "macromolecular solvents," enabling molecular dissolution of the drugs within the polymers. Large molecules, such as peptides, proteins, and nucleic acids, can be incorporated into the CAPRO polymers as particulate dispersion. In relation, they are particularly suited for combination drugs, providing spatially segregated compartments for various APIs within the same dosage form.

### Formulation

Formulation using the CAPRO polymers can be very simple. The loading of drugs in the CAPRO polymers can be accomplished by admixing with or without solvent at moderate temperatures. Solvent-free formulation has the advantage of eliminating the concern of residual solvent in the final drug products and any associated toxicity. Moderate temperature during formulation alleviates the potential risk of heat denaturation and decomposition of certain fragile APIs. The "macromolecular solvent," ie, the CAPRO polymer, can be designed to bind to APIs through multiple sites of molecular interaction. Such cooperative binding imparts greater capacity of solubilization and stabilization of the API, resulting in exceptionally higher loading than what is achieved using simple small molecular solvents.

### Scaling-Up & Manufacturing

The synthesis of CAPRO polymers is highly scalable. The CAP-O series is syn-

thesized in three steps. The CAP-A series (containing acetal linkers) is synthesized in a single step. Synthesis can be conducted either in bulk without solvent or with USP class 3 solvents under moderate temperatures. The raw materials used for synthesis are common commercial compounds. We have developed GMP synthesis and purification protocols to manufacture CAP-O series of polymers in 100- to 200-g scale. Manufacturing of CAPRO-formulated drug products can be conducted using conventional admixing devices or standard spray drying apparatus. Furthermore, CAPRO polymers capable of forming structured liquids can be manufactured via 3D printing using either temperature-induced solidification and/or chemical reactive cross-linking methods. Tableting of CAPRO polymers with API is also possible in the presence of appropriate excipients and particulates.

### Storage

CAPRO polymers bind to APIs through specific molecular interactions, keeping them solubilized and preventing crystallization during storage. API stabilization can also be augmented by the CAPRO polymers' capacity of forming structured liquids, which greatly reduces the molecular mobility of the APIs within "gel-like" matrices. Water-sensitive, fragile APIs can be protected from hydrolysis and other forms of degradation by encapsulation within hydrophobic CAPRO polymers, whereas water-soluble biological APIs can be stabilized within hydrophilic or amphiphilic CAPRO polymers.

### Administration

The CAPRO polymer platform is designed to adapt to various routes of drug administration. Due to the fact that CAPRO polymers are viscous liquids, CAPRO-formulated drug products can be injected locally into the skin or muscle or ocular sites, to form long-acting depots that release drugs sustainably. In addition, certain CAPRO polymers can form emulsions of micro or nano-size droplets or particles and thus can be injected systemically.[18] They also can be applied topically to the skin or other mucosal tissues, such as nasal, buccal, sublingual, rectal, vaginal sites, and enhance the permeation of APIs across these tissue barriers. They can also be adapted to form various oral dosage forms, such as tablets, capsules, gels, and emulsions, and be combined with existing excipients for oral drug delivery.

### *In Vivo* Action

As "macromolecular solvents," CAPRO polymers can enhance the solubility and stability of poorly soluble drugs, resulting in more efficient absorption and higher bioavailability. The CAPRO polymers can undergo pre-programmed erosion and degradation to achieve either sustained long-term drug release, or modified release that maximizes drug absorption and efficacy. Micro and nano-droplets of CAPRO polymers can facilitate the intracellular uptake of drugs by specific cell types and the intracellular release of drugs within subcellular compartments. Importantly, the CAPRO polymers themselves are constructed from biocompatible building blocks such as PCL and they break down into nontoxic products, which ensures safety for human use.

## SUMMARY

TREKKA Therapeutics flexible and versatile CAPRO polymeric drug delivery platform has the potential to enormously impact healthcare. Achieving delivery of poorly soluble drugs and biologics will enhance the efficacy of a wide range of therapeutics for the treatment of a wide range of diseases. CAPRO represents a new and better class of excipients and will provide a new avenue for research and development teams that are dealing with bioavailability and efficacy challenges with new or existing compounds. ◆

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## BIOGRAPHIES

**Bob Wieden** is the President & CEO of TREKKA Therapeutics, LLC, a spin-off company from the University of Minnesota, that was formed to commercialize and develop advanced polymeric biomaterials to improve the efficacy and safety of drugs. He leads the overall strategy and commercialization efforts to bring this disruptive CAPRO™ technology solution to market to improve the patient experience and potentially patient outcomes. He is a growth-oriented business builder that has led a plethora of new ventures for Fortune 500 and private enterprises to fill "gaps" in unmet markets and looks to drive new therapeutic concepts to disrupt existing marketplaces. He can be reached at bobw@trekkatherapeutics.com.

**Dr. Chun Wang** is an Associate Professor of Biomedical Engineering, University of Minnesota. He is a Co-founder and CSO of TREKKA Therapeutics. He earned his PhD in Bioengineering at the University of Utah and was an NIH postdoctoral fellow at the Massachusetts Institute of Technology. He was a recipient of the National Science Foundation CAREER Award, Wallace H. Coulter Foundation Early Career Translational Research Award, and McKnight Land-Grant Professorship. He served on the editorial boards of the Journal of Controlled Release (2006-2016) and Advanced Drug Delivery Reviews (since 2010). He has published 100 peer-reviewed research articles and reviews and has given over 120 invited talks. His research interest is in polymer-based therapeutic biomaterials with applications in controlled drug delivery, immunotherapy, medical devices, and regenerative medicine.

# HUMAN FACTORS STUDIES

## Human Factors Studies During a Pandemic: How One Company Adapted to Covid-19 Restrictions

By: Miranda Newbery

### INTRODUCTION

Because human factors and usability engineering rely on the interaction between people and medical devices, both activities were vulnerable to lockdown measures and social distancing guidelines when the pandemic began, thereby threatening the completion of medical devices currently in development. Human factors testing allows device designers to understand the ways people: perceive information from a device; interpret the information and make decisions about what to do; and how they manipulate the device, its components or its controls.[1] Though it is possible to carry out use risk assessments, expert reviews and device comparisons – which do not require contact with end users – these cannot fully replace first-hand user feedback. Observing users interacting with a device provides reassurance the devices are safe and effective for the intended users, uses, and use environments.

### PLANNING HUMAN FACTORS STUDIES DURING COVID-19

To allow for continued medical device development, human factors engineers were faced with the challenge of adapting their methods to comply with local restrictions and maintain participant safety. Halting human factors testing was not an ideal solution, given that there was little certainty about how long the situation would last. Owen Mumford Pharmaceutical Services had conducted a large-scale formative study in January 2020 to test a platform autoinjector, and needed to confirm the design changes made after the study had improved the design with respect to the user interface. Rather than cancelling the follow-up usability study, we decided to adapt the study design.

### ENSURING REPRESENTATION FOR PLATFORM DEVICES

For platform devices, it is especially important the user cohort is as inclusive as possible. Platform products are designed to accommodate a range of delivery capabilities, and formulations applicable for multiple therapy areas, and so the specific user group is not known. The sample user group for testing must therefore be as broad as possible, to ensure the needs of patients with varying physical and cognitive abilities have been taken into account. Recruiters for human factors studies must be given a thorough brief so they understand the process and aims of human factors studies, and can properly inform prospective participants.

In this example, we aimed to test patients who were likely to have the most difficulty using the product. The cohort included people with musculoskeletal and neurological conditions, and people with visual and hearing impairments. We also made sure to include both children and adults, and healthcare professionals. Not all participants had injection experience, so we could observe whether inexperienced people also found the product intuitive and easy to use. To facilitate travel during a lockdown situation, and to aid mobility-impaired participants, the chosen venue was in a suburban area with parking, and we encouraged participants to walk or drive rather than use public transport.

## PROTECTING PATIENTS FROM INFECTION & INJURY

Maintaining patient safety during a pandemic extended the length of the study. A risk assessment was carried out in advance and any risks mitigated. Before each session, the testing room needed to be cleaned and ventilated. Prototypes were all packed at least 3 days in advance of the study by engineers wearing PPE, and were kept sealed until needed. Because moderators could not hand out prototypes – 15 autoinjectors in this case – they were numbered and placed in color-coded sections of a set of trays, so the moderator could easily direct participants during the session. Apart from infection risk, we also needed to account for the risk of needlestick injury while participants handled the autoinjectors; moderators were highly vigilant, and there were no incidents.

## CREATING A CLEAR STUDY DESIGN

Because there were multiple prototypes to be tested and compared, it was imperative for the study protocol and discussion guide to be as clear and simple as possible, especially as the moderator would have to describe actions they would normally demonstrate for participants. For this study, we also needed to gather anthropometric data to inform the product's design, so the moderator described how to use the equipment to participants. Overall, we focused on evaluating key parts of the device design to avoid complication.

## CAPTURING PARTICIPANT FEEDBACK

The rapport between participants and moderators is an integral part of human factors studies as participants should feel at ease, and free to interact with the device and express their views. Any pressure can constrain this freedom and affect the study results. At the same time, the moderator, client, and other observers need to be able to see and hear feedback first-hand. Fortunately, participants were pleased to be outside of their homes and this helped to build rapport. They appeared to enjoy testing the products and providing feedback.

Live video streaming with the help of a local video company allowed close observation throughout testing. We needed to be able to view the autoinjector up close as participants handled the product and clearly hear their reactions. For this, we used production-equivalent cameras that could transmit high-definition video feeds simultaneously. The Picture in Picture (PiP) capability enabled a close-up view of the autoinjector going into the injection pad, and a wide view of the participants and their interaction with the device. High-quality microphones meant we could capture audible feedback and participant responses. We used Microsoft Teams to stream the content so representatives from Owen Mumford were able to ask the moderator questions about participant behavior during the sessions. The recordings were made available after the study so they could be analyzed.

## LAUNCHING THE FINAL PRODUCT

The modified study was a success, helped by our participants' flexibility and their ability to adapt to the unusual conditions. We observed the restrictions, and changes did not seem to impact the flow of the study, participant recruitment, or how the participants interacted with the autoinjectors. The Owen Mumford team was able to progress to the design freeze stage, ready for product launch in late 2021. As circumstances continue to evolve, human factors studies are likely to require careful planning and modification, as well as additional risk assessment. However, it is certainly possible to conduct successful in-person studies and continue to safely bring new medical products to market. ◆

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## BIOGRAPHY

**Miranda Newbery** is a creative human factors and user research consultant with over 10 years of product development experience. She firmly believes in putting the user at the heart of the design process and combines her expertise in medical devices, human factors regulations, design, and user research to creatively identify unmet needs. She has a wealth of experience in combination drug delivery devices. She originally studied Mechanical Engineering at Cambridge University and Industrial Design at the Royal College of Art. She is a chartered ergonomist with the CIEHF and founded Inspired Usability in 2016. She previously worked as the lead human factors consultant at PA Consulting and The Technology Partnership in Cambridge, UK. She also runs the Medical Human Factors Network, UK, which is a networking group for human factors professionals in the UK.

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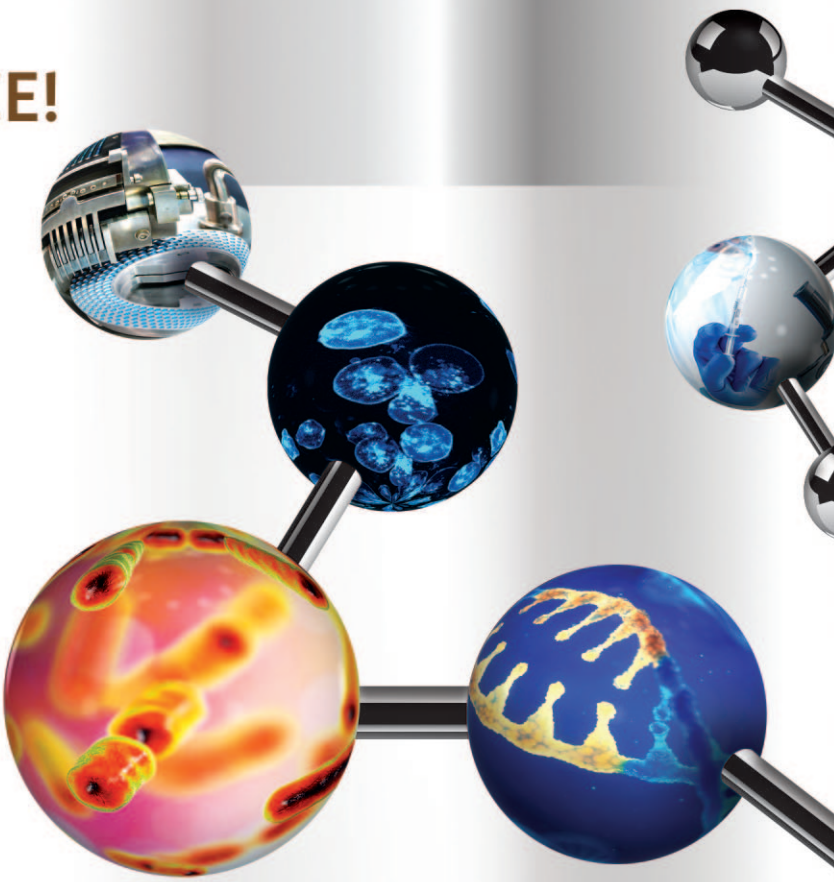

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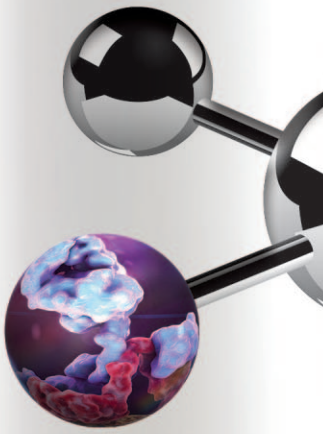

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# ARTIFICIAL INTELLIGENCE

## Attempting to Speed Up Vaccine Development to Combat the Next Pandemic

By: Lars Wegner, MD

### INTRODUCTION

The Danish company Evaxion Biotech A/S is using state-of-the-art mathematical modelling and algorithms in a bid to transform drug discovery and development. In the wake of the huge impact Covid-19 has had around the world, Evaxion is now applying this approach to vaccine development to prevent the next pandemic.

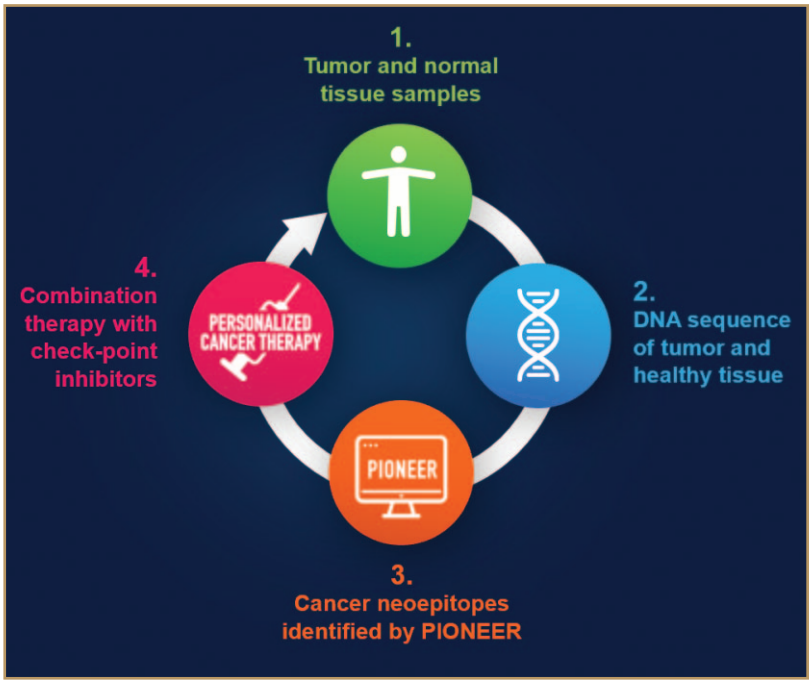
Since 2008, Evaxion's scientists and software engineers have developed a platform that uses artificial intelligence (AI) to track the traces left by antigens that evade the immune system. These state-of-the-art in silico tools integrate biological data, AI, and supercomputing, aiming to transform and accelerate the way immunotherapies are discovered and developed. This approach underpins Evaxion's pipeline addressing two of the biggest health threats in the world, infectious diseases and cancer.

Evaxion is now leveraging its technology and expertise with a new platform, RAVEN, with the goal of rapidly responding to emerging viral diseases. RAVEN has been designed to quickly identify novel vaccine candidates against an emerging or mutating virus, which may be rapidly advanced into clinical development based on Evaxion's unique manufacturing process. Evaxion believes this exciting novel platform holds the potential to limit or prevent the significant human impact and cost of a disease that seemingly comes out of nowhere and spreads around the world.

### SPEEDING UP TRADITIONAL DRUG DEVELOPMENT

Predicting the properties of proteins and epitopes that elicit a desired immune response is a complex undertaking. Traditional protein drug development requires repeated rounds of manual design of molecules, chemical synthesis, and experimental testing. It is expensive, takes a long time, and comes with high failure rates.

Evaxion's proposed solution to the development of novel immunotherapies and vaccines is based on three platforms, EDEN, PIONEER, and RAVEN, which Evaxion believes are capable of accurately predicting the key



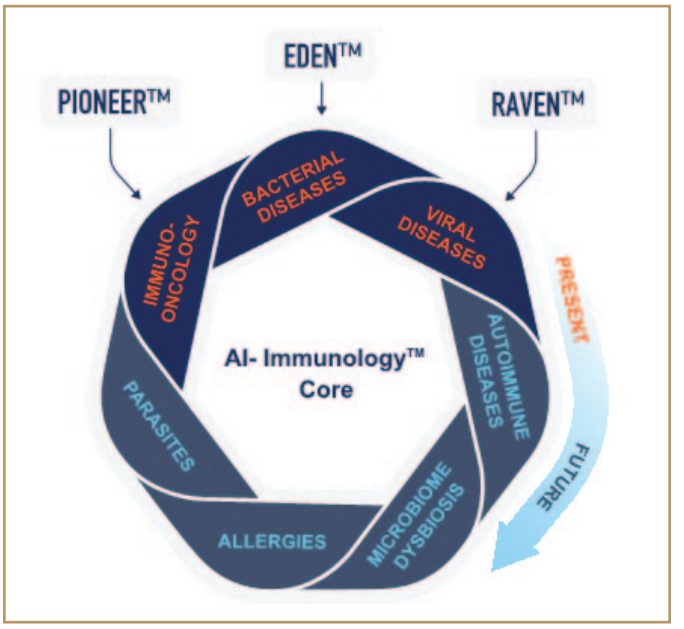
properties of proteins and epitopes to enable the rapid development of novel, personalized immunotherapies and vaccines.

This enables Evaxion's discovery teams to design and synthesize optimized proteins and epitopes from the start, which potentially significantly reduces the time and cost needed to identify candidates for development and, through the predicted biological functionality and effect of the protein or epitope target, may increase the chances of these entering clinical development and eventually reaching the market.

The RAVEN platform combines elements from EDEN and PIONEER and has been designed to select the best targets for a vaccine to rapidly respond to an emerging or mutating viral disease. In creating the viral-specific RAVEN platform, Evaxion took the ability of EDEN to identify B-cell antigens and combined it with the algorithms from PIONEER to identify T-cell epitopes to optimize the target antigens. The project is backed by the Danish state's Innovation Fund Denmark with funding of DKK 5 million (USD800,000) to build a response platform to quickly identify the best targets for future viral vaccines that, once identified, can be rapidly produced.

Evaxion already had the relevant algorithms, so the challenge was training the algorithms to be viral specific, addressing the hurdles in developing vaccines by including both T-cells and B-cells. The company is now pursuing proof-of-concept in coronavirus to be able to respond to future emergent coronaviruses.

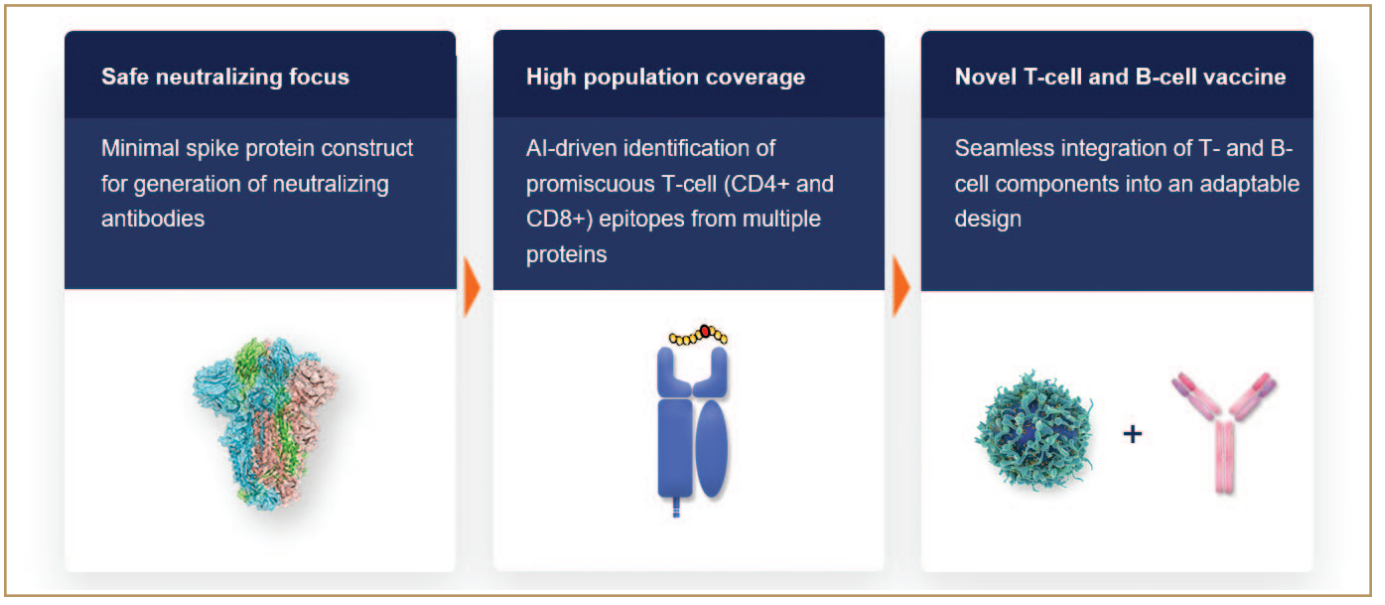
The main aim is to have a rapid response platform to be much better prepared to address future pandemics. This will be based on a discovery and manufacturing process that can create potential vaccines in as little as 11 weeks from initial concept to first human dosing, and then developing these quickly through clinical trials, potentially in partnership with a larger vaccine company.




## A NEW MANUFACTURING TECHNOLOGY

To extend the potential of RAVEN, Evaxion will be combining it with a new manufacturing technology to tackle the production bottleneck of current manufacturing technologies and enable rapid scale up for commercial production.

This technology, known as µLOT®, is developed by SB3000, a Danish company dedicated to developing green manufacturing solutions for continuous manufacturing in the pharmaceutical in-




dustry. The expectation is that the µLOT technology for continuous manufacturing (e.g., in hospitals) of peptides may allow for acceleration of design, development, and supply.

The manufacturing process will be developed at scale during pre-clinical studies and, upon validation, Evaxion expects that this method will be scaled up and moved straight into commercial production with no further development required, at a fraction of the traditional manufacturing cost.

Because µLOT-enabled facilities are modular and a fraction of the size of traditional batch facilities, they have the potential to be easily transported to sites and hospitals around the world. This is becoming particularly important as more and more countries see securing internal supply of essential medicines as a key strategic element of a nation's security.

## IDENTIFYING ANTIGENS IN HOURS

The antibacterial platform, EDEN, is the basis of developing RAVEN. EDEN has been shown to identify novel, bacterial vaccine antigens that trigger protective immune responses against a broad range of bacterial sub-strains, and it has done so in as little as a matter of hours. Evaxion believes that EDEN will allow the company to rapidly discover novel vaccines with optimized profiles and, potentially, a higher likelihood of success in development.

Taking advantage of the rapid increase in big data from modern, high throughput sequencing studies, EDEN utilizes proteomes from clinically relevant pathogen strains as input. With specialized AI methods, EDEN targets immune evasion strategies of bacteria and outputs a list of proteins ranked by their capability to induce a highly protective immune response.

As well as being accurate, fast, and low cost, EDEN has the ability to identify novel protective vaccine proteins in an unbiased way. Evaxion believes that EDEN is broadly relevant to multi-drug-resistant pathogens, preserving use of antibiotics. Evaxion has infectious disease pipeline programs that target *S. aureus* and *P. aeruginosa*. Evaxion believes that the protective antigens identified by EDEN have the potential to prevent diseases caused by both resistant and non-resistant strains.

Evaxion believes EDEN further enables the company to investigate any bac-

### APPLYING AI IN IMMUNO-ONCOLOGY

While the RAVEN and EDEN platforms focus on infectious diseases, PIONEER is Evaxion's fully automated immuno-oncology platform, using sophisticated algorithms to identify and select those neo-epitopes (tumour-specific mutations) that Evaxion believes are most likely to generate a profound anti-cancer immune response. These newly identified neoepitopes are then applied in a therapeutic strategy in an effort to deliver personalized, synthetic neoepitopes to patients in as little as a few weeks.

Evaxion has improved the prediction power of PIONEER to supersede current, state-of-the-art technologies and it is being utilized to build a unique pipeline of personalized cancer immunotherapies using different delivery modalities. Evaxion is rapidly expanding its preclinical pipeline and demonstrating the ground-breaking potential of PIONEER.

terial infectious disease using innovative methods. Evaxion believes that within a matter of weeks, new candidates can be generated and tested in animals, significantly accelerating the speed of vaccine development, as well as reducing the cost and risk associated with discovery and preclinical development.

The threat of bacterial infections is growing exponentially, and by 2050, it is expected that more people will die as result of infection by multi-resistant pathogens as from cancer.[1] The potential impact of EDEN may be to directly prevent disease caused by resistant and non-resistant strains of the bacteria. This will in turn reduce the use of antibiotics.

## BETTER PREDICTIONS

The great advantage of AI in drug development is that it makes no assumptions about what is right and wrong. This means it can make predictions that scientists would not necessarily make, because they had already excluded something, for example, about the immune system and how it reacts, which may not be conclusively proven.

The system can be trained to spot connections, such as in structures of proteins, which are not possible with standard approaches. Conclusions may come within hours, thereby quickly providing you with something to test. Once AI is integrated into drug discovery, you can also feed data back into the system to improve it further.

Evaxion is one of the first companies to start generating clinical data on products identified by AI. Evaxion believes that this process has the potential to remove even more risk from the developing pipeline and clinical programs, enabling multiple therapies from each of the company's individual platforms. In the case of Evaxion's adjuvant immunotherapy vaccine, EVX-02, it took less than 18 months from the initial concept to being ready to test in patients. Evaxion believes that the process can be reproduced, as can the technology.

## LIMITING THE FALLOUT

When Evaxion started in 2008, it faced some initial skepticism in the marketplace on the role of AI in drug discovery. This changed around 2016, with the first success stories about the role of AI in the development of small molecules.

Evaxion's approach is methodical, rigorous, and committed. Evaxion spent a lot of time building its systems – addressing the specific biological issue that needed to be solved, then building the first version, testing, feeding in data, and improving. The most important part of this process was to be able to successfully combine expertise in AI, immunology, and drug development and taking the time to develop the platform comprehensively.

COVID-19 has provided a significant demonstration of the ability of infectious diseases to fundamentally threaten the world. Evaxion believes the best way of combating infectious diseases is through prophylactic vaccines, not therapies. By enabling the rapid development of vaccines against future disease threats, Evaxion hopes to significanty reduce the fallout when the next pandemic hits. ◆

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## BIOGRAPHY

**Dr. Lars Wegner** is Chief Executive Officer and a founding investor of Evaxion. He began his career as a medical doctor and worked for several years as a clinician. He has extensive experience in the vaccine industry, first at Pfizer and then for 10 years as a member of senior management at the immuno-oncology and vaccine company Bavarian Nordic. He has previously been involved in multiple start-ups and early ventures.

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Drug Development
EXECUTIVE

Stephen Rumbelow, PhD

Life Sciences
Research Fellow

Croda Inc.

CRODA

# Croda: Solutions for Your High Value Drug Products

Formulating a drug for parenteral delivery comes with its fair set of challenges. Aside from a high level of sensitivity to external factors like light and heat exposure, these large and complex drugs are prone to degradation when exposed to various chemical species. For this reason, these applications typically require extremely pure and highly functional excipients to stabilize the drug and aid in its delivery. Croda's range of Super Refined™ excipients is designed with this in mind. The company offers a wide variety of chemistries with exceptionally low impurity profiles, yielding improved oxidative stability for both the excipient and any solubilized drug. *Drug Development & Delivery* recently sat down with Dr. Stephen Rumbelow, Life Sciences Research Fellow for Croda Inc., to discuss polysorbates, a key excipient used for stabilizing drug molecules in injectable dosage forms.

**Q: Can you tell us a little bit about your background and experience working with customers formulating with biologics?**

**A:** I am the Life Sciences Research Fellow for Croda Inc, with responsibility for developing external partnerships with companies, universities, and research institutes. Previously, I was the Research and Technology Manager for the Innovation Support and Health Care teams for Croda Inc, where I managed a Health Care team responsible for generating new high purity excipients for the pharmaceutical industry. This includes products for all major delivery routes and applications, ranging from emulsifiers and dispersants through to solvents and permeation enhancers. Additionally, the team is also very active in generating accompanying performance and application data for such applications, with a particular emphasis on the impact of excipient purity on drug delivery and performance. Our Innovation Support team closely assists in these activities, along with supporting other businesses within Croda. In my current and more recent roles, I actively work on a

number of collaborative projects with major companies in the pharmaceutical industry, covering many aspects of the use of polysorbates in injectable formulations. Customer collaborations focus on areas such as the impact of excipient purity on formulation stability and more recently, benchmarking the performance of these excipients against similar materials in this application. It's worth noting that Croda also supplies a number of other materials for use in injectable formulations, including those for oncological treatments, and we have been involved in numerous studies demonstrating the importance of excipient purity on the stability of active pharmaceutical ingredients (APIs) for oncology. Furthermore, with the recent purchase of Avanti Polar Lipids, our portfolio and expertise has expanded considerably in the field of lipid-mediated delivery, which addresses the needs of a widely diverse range of APIs, from small molecules to peptides and gene therapy agents.

**Q: Croda is known for making polysorbates; how are polysorbates used in injection applications?**

**A:** Polysorbates 20 and 80 have a long track record of safe use and are listed on the FDA's Inactive Ingredient Database (IID) list for injectable applications, typically being used in biotherapeutic formulations at concentrations ranging from 0.001%-0.1%. In the case of biologics, which are typically administered via injection, these excipients have been well recognized by the industry as important and highly effective stabilizers for proteins against interfacial stresses, even at these very low concentrations. These stresses can occur from a variety of sources, including air/liquid interfaces (particularly with shaking), surface interactions (with the internal surfaces of processing equipment and the vials themselves) and even ice/liquid interfaces (as might be encountered in freeze/thawing processes), all of which can cause surface adsorption, protein aggregation, or precipitation. Polysorbates are very effective, not only in mitigating against these problems, but in their ability to stabilize therapeutic proteins and prevent aggregation. Similarly, the surfactant properties of these excipients can be very effective in facilitating the re-dissolving of freeze-dried formulations, too, in terms of both wetting and prevention of clumping and aggregation.

**Q: Can you speak to the implications of excipient grade on formulation stability?**

**A:** This is very important, particularly considering the risks (and financial implications) associated with potentially losing biological efficacy for biological APIs that are both expensive to develop and highly prone to degradation. We always recommend using high purity variants of these products instead of the standard compendial grades, even if extra microbiological tests might have been performed on them. This is because the impurities in excipients can impact API and formulation stability in a number of ways. This is a topic which has been highlighted in numerous peer-reviewed scientific publications. The formulator should pay particular attention to such impurities as residual peroxides, which can lead to oxidative degradation, and metals, which can catalyze such reactions. Residual aldehydes can also be of concern because these, too, can react with various reactive groups on the amino acids, resulting in a loss of efficacy. Finally, residual free fatty acid levels can also play a critical part in determining the likelihood of the onset of the formation of precipitates, which can, in turn, result in the appearance of cloudiness and, ultimately, the rejection of batches of formulations. It is well recognized that these excipient impurity issues can be successfully addressed using a combination of carefully selected high purity starting materials, in addition to well-controlled and mild processing conditions. In the case of Croda's Super Refined™ range, this is further supplemented with a final proprietary purification stage that significantly decreases these impurity levels further. Super Refined™ excipients are well recognized and widely used in biotherapeutics, as well as in other application areas in the pharmaceutical industry where API stability is a chief concern.

**Q: Can you speak about the implications of polysorbate composition on formulation stability?**

**A:** One of the reported concerns with biotherapeutic formulations has been the carryover of residual lipases from CHO cell-based cultures used to produce monoclonal antibodies, which can then, under certain circumstances, occasionally result in the hydrolytic degradation of polysorbates. Polysorbates are a complex mixture of chemical species by nature of their manufacture: a multi-step process based around naturally derived sugars and fatty acids followed by ethoxylation. In the case of Polysorbate 20, if this hydrolysis proceeds to a significant extent, this can sometimes lead to the liberation of

significantly high enough levels of higher molecular weight (>C14) fatty acids which, having poor water solubility, can precipitate out and lead to the appearance of cloudiness. However, there are clearly several ways to minimize the risk of such an issue, ranging from minimizing such carryover of lipases, through to selecting polysorbates of the appropriate grade and purity which have lower levels of residual-free fatty acids from the start.

Despite their inherent complexity, it is quite possible to manufacture polysorbates with a high degree of reproducibility using the appropriate manufacturing controls and careful selection of raw materials of consistent quality. This can be readily verified, not just from the certificate of analyses for individual batches, but from more sophisticated chromatography and spectrometry techniques, which show considerably more detail on their composition, down to the relative amounts of certain classes of compounds. Super Refined™ polysorbates are manufactured with these conditions in mind, which also helps considerably with batch-to-batch consistency, something formulators are actively looking for when selecting an ingredient supplier. Moreover, it is also possible to produce a custom variant of Polysorbates 20 and 80, in which the fatty acid levels distribution have been adjusted to further minimize this risk. Such products are now commercially available.

**Q: Are there any best practices for handling materials going into injectable formulations?**

**A:** There are several best practices when handling polysorbates and, for that matter, any high purity excipient going into injectable formulations. These products are typically supplied in sealed containers under nitrogen to ensure they retain their high quality and protect them from degradation. Therefore, we prefer that end users select the appropriate package size so that they can ideally use all the material in a single use if possible. High purity, highly differentiated products are typically available in a range of pack sizes in order to accommodate this. Croda offers materials in a wide assortment of packaging, including as low as 250 gram bottles. For users that find themselves wishing to retain product containers that have been opened, we strongly recommend re-sparging with nitrogen and can supply detailed procedures on how to perform this effectively. This is one of the most important considerations when handling these materials in this particular application area. Additionally, these products are typically supplied in metal containers in order to prevent light exposure, and we recommend that the customer stores them in their original containers. We would also discourage any practice of transferring high grade excipients that have been manufactured to meet high purity standards into secondary containers, as this can result in the quality of the excipient being compromised.

**Q: While polysorbates have a long history of use in the parenteral space, are there situations where they wouldn't be used?**

**A:** We are not aware of any situations in which polysorbates cannot be used with biotherapeutic formulations, and it should be noted that they have a long track record of safe and effective use. There is some interest in the industry to consider alternative chemistries, but questions remain about their effectiveness and versatility, and any such materials would need to go through the FDA approval process.

**Q: Any last thoughts around your experience with injectables?**

**A:** The injectables market is slated to grow more rapidly than ever, with therapies becoming more personalized and drugs becoming more innovative and efficacious. However, with growth comes increasing concerns of drug stability, degradation, and delivery. As a result, it's important for formulators to work with their suppliers rather than just purchasing product from them. Partnerships with our customers and working on collaborative projects allow us to better understand the usage of our materials and create new and innovative products. Our excipient solutions, whether it be our Super Refined™ range of high purity ingredients, aseptically manufactured vaccine adjuvants, or highly functional specialty lipids, allow us the breadth to help our customers find the best solution for their injectable application. Our Super Refined™ range is ever expanding as well, and a number of our products come as solutions stemming from our collaborations with customers. We're heavily investing in this growth as a business as well, with new expansions at our sites, the introduction of new technologies and capabilities, and the growth of our teams. It's an exciting time to be part of the pharmaceutical space, and Croda strives to be a key player at the forefront of innovation. ◆

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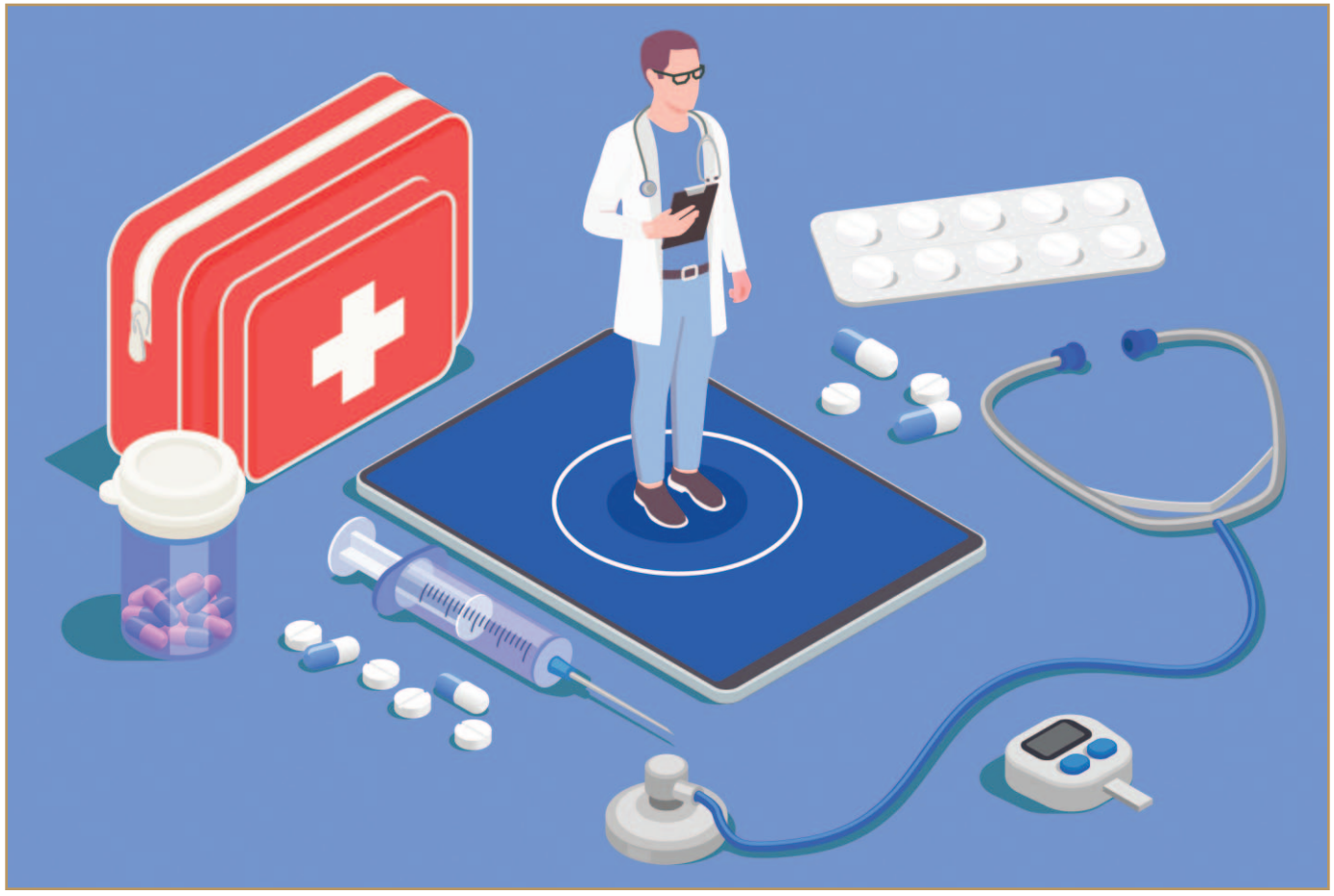
# Five Perspectives on Connected Drug Delivery Devices

By: George I'ons

## INTRODUCTION

The global pandemic has heightened the urgent need to reduce the strain on healthcare systems and resources, and reinforced the benefits of teleconsultations and patient self-administration in alleviating some of this pressure. In fact, remote services appear as one of the top three benefits of healthcare digitalization, according to a recent study.[1] Enabling patient self-management where possible frees up time and resources for health services. Hospitals and clinics that do not take full advantage of this opportunity run the risk of being over-run and unable to withstand growing demand.

Remote patient monitoring is already well-established for patients with chronic respiratory conditions and diabetes. More recently, however, digital capabilities are being developed in the area of drug delivery. Our own research predicts that this will be an area of strong development in the next 5 years – with the global market for connected drug delivery devices (both for injection and inhalation) expected to reach $706 million by 2025, rising from $225 million in 2020.[2] Enabling successful adoption of these devices, however, will largely depend on a number of key stakeholders. Payers, clinicians, patients, regulatory authorities, and pharmaceutical companies



all play a fundamental role in shaping the future of connected drug delivery devices.

For pharmaceutical professionals, this discussion offers insight into the factors driving the development and adoption of connected drug delivery devices and examines the varying perspectives held by relevant healthcare stakeholders. To provide maximum value to patients, clinicians, and payers, pharmaceutical businesses need to ensure that digitally-enabled drug delivery devices deliver several key capabilities. Uptake in connected device use greatly depends on meeting these expectations. Given the potential that connected devices hold to improve healthcare outcomes and services, a thorough examination of all moving parts is valuable and may help to get it right.

## WHAT'S IN IT FOR PHARMACEUTICAL COMPANIES?

Before looking at the advantages and expectations for other stakeholders, it's worth considering the value-add for pharmaceutical companies. Tracking and managing adherence with the support of connected devices can improve patient outcomes. Improved adherence reduces the risk of costly drugs such as injectable biologic therapies going to waste. Furthermore, with a number of pharmaceutical and medical device companies beginning to offer wider services such as training, adherence monitoring, and benefit tracking – in addition to the drug product itself – connected devices can facilitate such services. By supervising patient adherence through connected devices, pharmaceutical companies can also better demonstrate value for money, which is a vital competitive differentiator.

## JUST WHAT THE DOCTOR ORDERED

For clinicians, the appeal of connected devices is their potential to optimize outcomes while counteracting staff shortages. Connected drug delivery devices use embedded electronics and sensors to relay information back to the clinician – including time, volume, and site of self-administration. This offers clinicians a valuable tool to better track patient adherence and understand the outcome of a treatment for each patient individually, using concrete data. Where necessary, it also allows the clinician to make any necessary interventions to improve poor compliance. This may be in the form of training, support, or education around the patient's condition and treatment.

## PAYERS' CHOICE

Whether they are health insurance providers or state healthcare systems, payers can also benefit from connected devices given they hold the potential to decrease overall healthcare costs. As they look to deliver maximum value for money from healthcare budgets, a society that is less dependent on healthcare services is favourable to their "outcomes-based healthcare" approach.

If patients are able to manage their own treatment more efficiently, this is likely to reduce the number of visits to hospitals and clinics. Connected devices help to ensure correct dosage and administration, thereby increasing the likelihood of a successful treatment that doesn't require costly secondary interventions. Connected devices reduce the effort required by patients to comply with the prescribed medication regime, as they offer reminders and adherence trackers. This means less wastage of costly medications including the increasingly prescribed injectable biologic therapies that insurers would need to reimburse.

Nonetheless, businesses will need to demonstrate to insurers and payers that connected devices produce measurable outcomes as a result of improved adherence, which may be challenging to prove without first deploying the products on the market.

## MOBILE PATIENTS

Connected devices provide patients with access to their own treatment data, enabling a deeper understanding of their condition and their body's response to the prescribed medication. Training programs on best practice for self-injection can be offered alongside remote monitoring, to ensure patients are aware of proper techniques and are equipped with the right information to safely carry out their own treatment at home, and to correctly use digital tools. This empowers patients to take control of their own health and allows them to integrate their medication regime more seamlessly into their everyday lives. With increasing patient-specific dosing in some disease areas, connected devices make space for a tailored regime that works best for the patient.

## THOUGHTS FOR MANUFACTURERS

While the benefits of data access for patients are evident, manufacturing companies will want to consider the amount of

information that is being shared with the patient through notifications. When designing a connected device, manufacturers should look to achieve a healthy halfway point where the frequency of notifications is not too imposing, and the level of detail or amount of information not too overwhelming. If not properly thought through, this could impact patient adherence. In fact, patient comfort and ease-of-use must be a priority from the very start of the device design process. Manufacturers will have to carry out mandatory Human Factors (HF) studies to ensure these two areas are thoroughly addressed and prioritised. Any potential risks should be mitigated and eliminated at this stage in order to optimize product usability.

The bottom line for manufacturers is that connected devices will need to be user-friendly for patients operating them at home and should therefore be designed with both patients and healthcare professionals in mind. Pharmaceutical companies selecting a connected device for their drug should ensure the medical device manufacturer has considered all usability aspects including those for device connecting, pairing, and data transfer.

## SAFETY, SECURITY & ENVIRONMENTAL REGULATORS

Connected devices will need to be interoperable with standard clinical information systems and robustly protected from data breaches. To make this possible, collaboration between regulators and market players will be necessary. Environmental regulations and objectives will also be important considerations in the development of connected devices. Drug delivery device designers are also under pressure to create products that enable connectivity but minimise wastage. Given that electronic components often contain rare-earth metals that are typically not properly recycled, device designers are acutely aware of the damaging environmental impact of entirely disposable connected devices, not to mention the cost.[3] With environmental concerns high on the world agenda, finding a sustainable hybrid approach will be crucial in the development of connected drug delivery devices. The ability to reuse parts of the device would be a good starting point. For instance, some designs may opt to offer disposable injection devices but coupled with a reusable connected "shell" section containing the electronic components.

Even as the vaccine rollout offers some respite to the battle with COVID-19, the need to alleviate pressure on healthcare services will outlive the pandemic, which has shone a light on the benefits of remote monitoring to better mitigate hospital occupancy levels. The potential benefits of connected drug delivery devices for all involved parties are manifold, but it's up to pharmaceutical companies and medical device manufacturers to ensure all elements have been considered in order to best meet the expectations of each stakeholder. A joint effort will be necessary to overcome a number of challenges, including data security concerns, environmental concerns, and regulatory requirements effectively. While growth within the connected device market shows no signs of slowing down, the extent of this growth and its long-lasting success will depend on a multi-faceted and collaborative approach. ◆

**Download a free copy of the OMPS paper – Well Connected – here: https://www.ompharmaservices.com/news-and-resources/connectivity-report/**

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## BIOGRAPHY


**George I'ons** is currently Head of Product Strategy and Insights at Owen Mumford having worked for the former OEM and now Pharmaceutical Services division of the organization since 2006. His current focus is on deciphering the rapidly changing pharmaceutical and biotech sectors in relation to their needs for combination products. In his previous roles in business development, he worked closely alongside R&D to develop devices for a variety of global pharmaceutical and diagnostic clients. Prior to Owen Mumford, he worked for Abbott in EMEA marketing roles in Germany, focusing on their diabetes business.

# DRUG DEVELOPMENT

## Simplifying the Drug Development Journey

By: Fran DeGrazio

### INTRODUCTION

Collectively, the top 20 pharmaceutical and biopharmaceutical companies spend approximately $60 billion on drug development annually.[1] Saving time in the drug development process creates opportunity to save expenses with the added benefit of delivering critically needed drugs to patients in a timely manner.

Timeliness, however, is not the only consideration. In conjunction with delivering efficacious new drugs, high quality, compliance, and patient safety are mandatory.

Because there are so many aspects to be considered, the ability to focus on simplifying the process as much as possible is important. Understanding the various resources available through industry, regulatory engagement, and suppliers is foundational to achieving this goal.

### REGULATORY DRIVERS

Over the last 10 years or so, many concepts have been introduced in an effort to facilitate improved concurrent quality and speed. The 21st Century Cures Act (Cures Act), signed into law on December 13, 2016, is designed to help accelerate medical product development and bring new innovations and advances to patients who need them faster and more efficiently.[2]

The latest iteration of the Prescription Drug User Fee Act (PDUFA), together with the 21st Century Cures Act, should accelerate the process, while mandating the US FDA to facilitate novel clinical trial designs. This flexibility is an example of allowing a trial design to be tailored and less complicated.

Andrew Powaleny of the US trade group Pharmaceutical Research and Manufacturers of America (PhRMA) is supportive of these kinds of measures as key to "keeping pace with the latest scientific advances in drug development." He says "Novel clinical trial approaches and drug development tools, such as adaptive trial designs, biomarkers, statistical and modeling approaches, as well as the use of real-world evidence have the potential to enhance the efficiency of the drug development and regulatory review processes."[3]

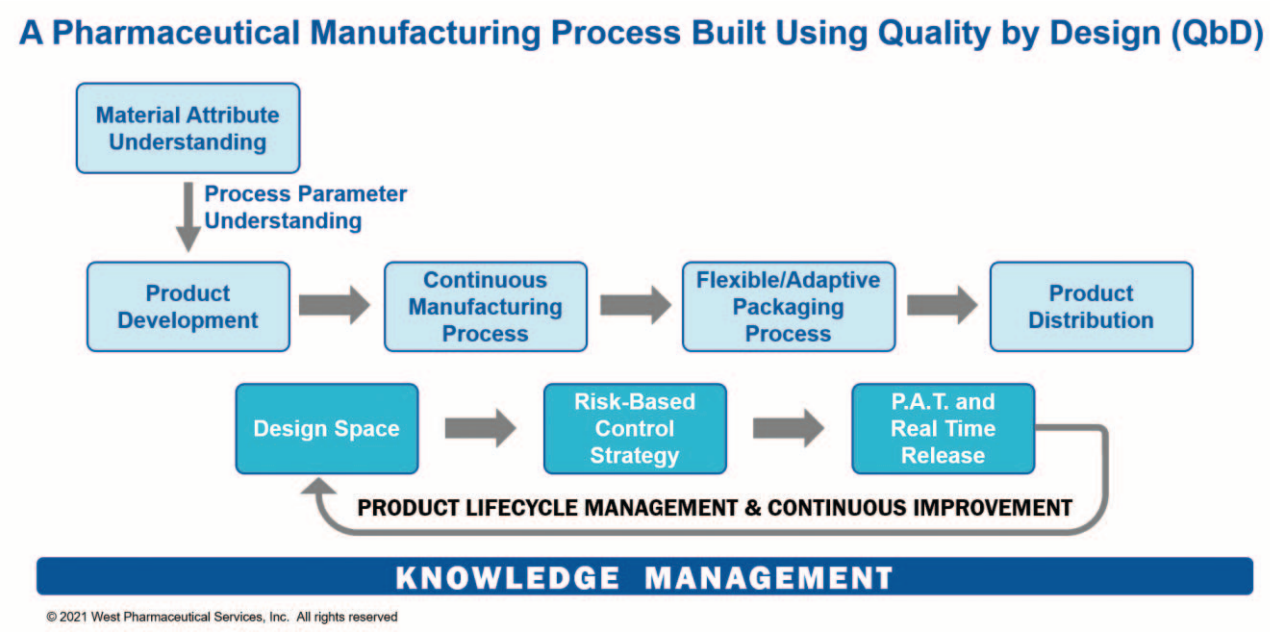
One of the priorities that the regulators want to focus on is more consideration of patients and their specific needs. The FDA is also encouraging drug and combination product owners to actively incorporate key stakeholders, such as patient advocates, researchers, drug developers, and healthcare providers, into the process to hear the patient's voice. This concept is called patient-focused drug development (PFDD).

Patient-focused drug development is a systematic approach to help ensure that patient experiences, perspectives, needs, and priorities are captured and meaningfully incorporated into drug development and evaluation.[4] The ultimate goal of drug development is not just to develop, but to commercialize and successfully reach patients.

One of the challenges in trying to achieve all of this in an efficient manner is the need to align endpoints around multiple global regulatory agencies, given that time-consuming and expensive trials are designed to fit multiple regulatory packages. This issue is helped somewhat by cooperation between agencies, often under the auspices of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH).

The ICH helps to set the agenda for Good Manufacturing Practice (GMP), as well as the design, conduct, safety, and report-

FIGURE 1




ing of clinical trials. ICH also encourages best practices through the use of the concepts explained in documents, including the following:

- ICH Q8 (R2): Pharmaceutical Development
- ICH Q9: Quality Risk Management
- ICH Q10: Pharmaceutical Quality System

These guidances form the basis for the approach to quality by design (QbD) for drug/biopharmaceutical products. Building a design space in development is foundational to the ability to institute innovation and other changes in the pharmaceutical manufacturing process. Figure 1 provides a high-level perspective of the quality system needed to support a more innovative manufacturing approach.

The QbD approach does not change regional regulatory requirements but can provide opportunities for more flexible approaches to meet them. Ultimately, this forms the basis to allow more effective change management that supports innovation within the process.

Integrating all these aspects together, therefore, allows the achievement of efficiency with improved quality, compliance, etc. Following this QbD process builds improved product and process understanding that allows more effective management of change.

The level of understanding directly relates to the amount of flexibility associated with change management. Figure 2, taken from the ICH Q12 guidance, visualizes this concept.[5]

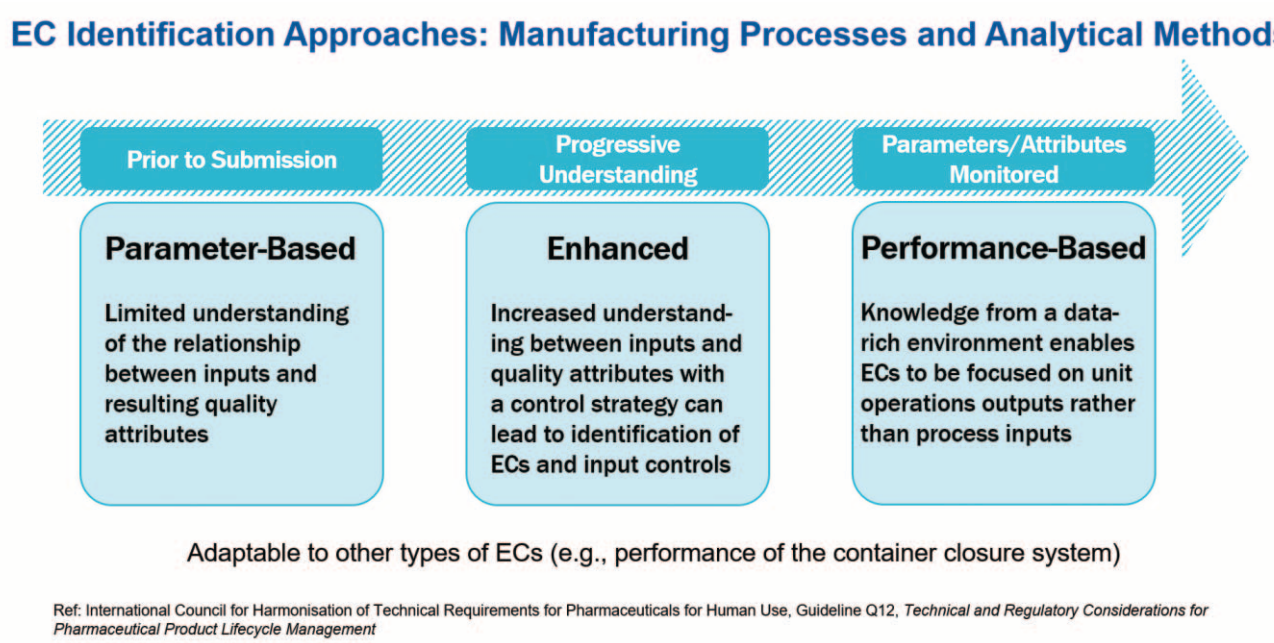
ICH Q12 – which provides guidance on lifecycle management – incorporates tools and concepts that allow one to leverage the earlier ICH guidances in order to be more effective in driving continuous improvement and innovation concepts. In addition to the ICH Q12 guideline, an implementation guidance will be introduced by the FDA in the near future to clarify how to implement the guidance within the FDA system. It will translate ICH post-approval categorization terminology to FDA supplement categorization and will provide guidance around established conditions (EC) relating to reporting categories, changes, and drug master files (DMF).

A thorough understanding of these regulations and guidances and their application forms the foundation to achieve the efficiencies the industry is looking for while assuring patient safety.

## TECHNICAL CHALLENGES

In addition to the regulatory challenges, the complexity of new modalities introduces new technical challenges. One of the most significant trends in the market is the growth of biologic-based treatments. Newer approaches have led to the increasing need to deliver higher than traditional volumes of biopharmaceutical-based products, such as monoclonal antibodies. A characteristic of these types of products is typically a higher viscosity because they are larger in physical size (< 100 atoms vs 25,000 atoms) compared to a typical chemically derived drug product. This leads to higher milligram per milliliter (mg/mL) concentrations. As these concen-

FIGURE 2




Ref: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, Guideline Q12, *Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management*

trations increase, the viscosity will increase.

Monoclonal antibody biotherapeutics are often administered by subcutaneous (SC) injection. Due to dose requirements and formulation limitations, SC injections > 1 mL are often required. Figure 3 provides data on the current fill volume ranges of marketed drug products.

Depending upon the volume that may need to be delivered to a patient, newer on-body delivery systems are now being utilized. These systems can deliver greater volumes over an extended time period. This provides much more flexibility vs a traditional prefilled syringe/autoinjector combination. Figure 4 provides an example of the West SmartDose® on-body injector.

New technology concepts must be developed to address the technical challenges faced when increasing dosage volume. One of these concepts is the use of a device to assist with the delivery of the drug to the patient. Bringing together this combination of drug and device, or biologic and device, leads to new challenges from both a technical and regulatory standpoint as these products are now considered drug-device combination products.

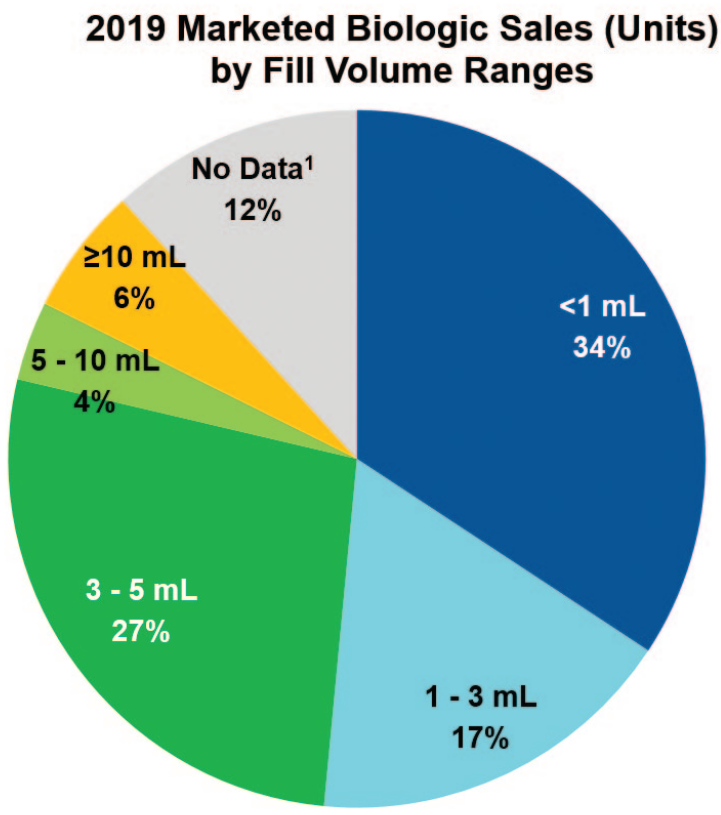
A combination product (CP) is defined by the FDA as two or more different products: a drug and a device; a biologic and a device; a drug and a biologic; or a drug, biologic and device. These products are composed of combinations that are physically, chemically, or otherwise mixed and produced as a single product; two or more products contained in a single package; or separate products that are cross-labeled to be used together.[6] Alignment of the unique drug/biologic and device regulatory pathways is essential for efficient development and effective commercialization of drug-device CPs.

Essentially, GMPs for drugs and biologics advocate the QbD framework, while devices follow design controls (DC) under the Quality System Regulation (QSR).[7-9] Design controls are a set of interrelated procedures to be incorporated into the design and development process. The QSR has been harmonized with the international quality management system standard, International Organization for Standardization (ISO) 13485 for medical devices and recognizes ISO 14971 for risk management.[10,11]

It is important to design a product to meet its claims and be developed based on principles of QbD and DC.[8] The quality target product profile (QTPP) and design inputs must be clearly defined to establish meaningful specifications to meet claims based on clinical performance.[12] This will include a host of interconnected factors, such as clinical setting of intended use, therapeutic moiety release and factors affecting pharmacokinetic characteristics, route of administration, dosage form, container closure/delivery system, and drug product quality criteria appropriate for the market.[13] Building quality into a drug-device CP encompasses understanding overall risks that are commensurate with patient needs starting at early development phases.[14]

One of the practical aspects of applying the regulations and performing actual combination product development is a "make or buy" decision when it comes to

## FIGURE 3




## FIGURE 4

the delivery device. A new internally developed device program – including device and clinical development, subassembly and final assembly, and testing – could take 5 years to develop and cost more than $50 million.[15] The alternative to a company developing its own delivery device is to leverage an already developed platform system from a third-party supplier. Doing this can often help to simplify the process of getting through regulatory approval and commercialization.

This kind of strategy not only addresses technical challenges but can also aid in expediting the development timeline. The ability to collaborate with a supplier that has experience with the development and commercialization of a device that has become a constituent part of a commercialized combination product is very beneficial. Considerations when evaluating device suppliers not only relate to the device itself but around other development services that can be utilized to complete the combination product, such as human factors, analytical testing, and regulatory support. These services are needed to facilitate appropriate development, commercialization, and lifecycle management.

Risk assessments that are inclusive of stakeholder engagement will facilitate alignment of the chemistry manufacturing controls (CMC) stage-gate process in order to enable timely development and lifecycle management. All phases involved in the process development should not proceed in isolation. The drug formulation, with the primary container closure system, may require multiple iterations to achieve the optimum balance of drug stability, manufacturability, and patient acceptance.[14]

With the growing number of biologic drugs in the pipeline, patient preference studies have shown that the use of subcutaneous delivery alternatives is significantly preferred over standard IV administration. In a study of 488 patients, 89% were shown to prefer a subcutaneous system.[16] Use of these systems addresses simplifying the administration aspects of delivering the drug to the patient.

All of the aforementioned various aspects are enablers for accelerating and simplifying development timelines. Historically, the pharmaceutical industry was very averse to change and innovation. Much of this was driven by the expectation that there was regulatory risk whenever there was change. This perspective is evolving. Several years ago, to address these concerns, the Center for Drug Evaluation and Research's (CDER) Office of Pharmaceutical Quality (OPQ) created the Emerging Technology Program. The purpose of this team is to encourage innovation in pharmaceutical product design and manufacturing.[17] This program enables industry representatives to meet with the FDA Emerging Technology Team (ETT) to discuss, identify, and resolve potential technical and regulatory issues regarding the development and implementation of a novel technology prior to filing a regulatory submission. Examples of the technologies evaluated by the ETT involved novel product technologies, manufacturing processes, or control strategies – such as new analytical technologies or process controls.

In 2017, the FDA published a guidance entitled Advancement of Emerging Technology Applications for Pharmaceutical Innovation and Modernization, which provides high level guidance to reinforce the concept of engaging early with the regulatory agency with new ideas and innovations.[18] This is a very visible way of making it easy for the industry to engage with the FDA directly to proactively deliver on new concepts.

## SUMMARY

Simplifying the drug development process can only be achieved by integrating innovation from both a regulatory and technical perspective. Understanding the opportunity that incorporating regulatory best practice opens is important across an organization. Using collaborators, such as knowledgeable suppliers and others to leverage their experience and capabilities, can also uncomplicate the challenges within the process. Suppliers have broad experience and typically have touchpoints across the industry – so they are aware of trends that arise and problems that can occur. Experienced and focused collaborators can provide guidance, support services, manpower, and intellect to make it easier to achieve all the goals needed in delivering a drug to a patient. The perfect collaboration allows organizations to work together seamlessly and allows open engagement to mitigate risks. The overarching goal of the pharmaceutical company along with its supplier/collaborators is to efficiently develop a product that meets all quality and regulatory requirements and ultimately meets the patient needs.

SmartDose® is a registered trademark of West Pharma. Services IL, Ltd., a subsidiary of West Pharmaceutical Services, Inc. ◆

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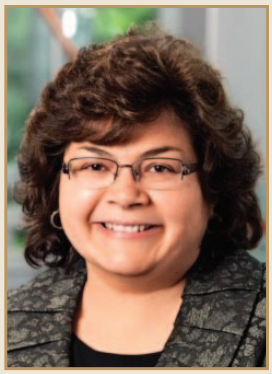

**Fran DeGrazio** has 35+ years of experience in the pharmaceutical packaging and delivery industry, with extensive expertise in injectable drug products, including vial container closure systems and prefillable systems for combination products. She has held numerous technical roles at West, including R&D, Quality & Regulatory, Technical Customer Support, Analytical Laboratories, and Scientific Affairs. In her current role as Chief Scientific Officer, she is responsible to leverage scientific and regulatory understanding across the enterprise. She received the Philadelphia Business Journal 2018 Healthcare Innovators of the Greater Philadelphia Region Award and the Healthcare Business Woman's Association Luminary Award for West in 2017.

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