

# Drug Development<sup>®</sup> & Delivery

September 2025 Vol 25 No 5

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## Faster, Integrated & Flexible Injection Devices

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# Injection Devices

“The future of injectable delivery is incredibly promising, particularly as we see rapid advances in combination product design, device technology, and patient engagement tools. From a development standpoint, I’m particularly excited about the growing alignment between formulation science and device engineering, which will allow for faster, more integrated development pathways and greater flexibility in delivering therapies that improve lives globally.”

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Contributor Cindy H. Dubin speaks with several companies who highlight how device developers are addressing various challenges while still ensuring precise dosage control and patient compliance.



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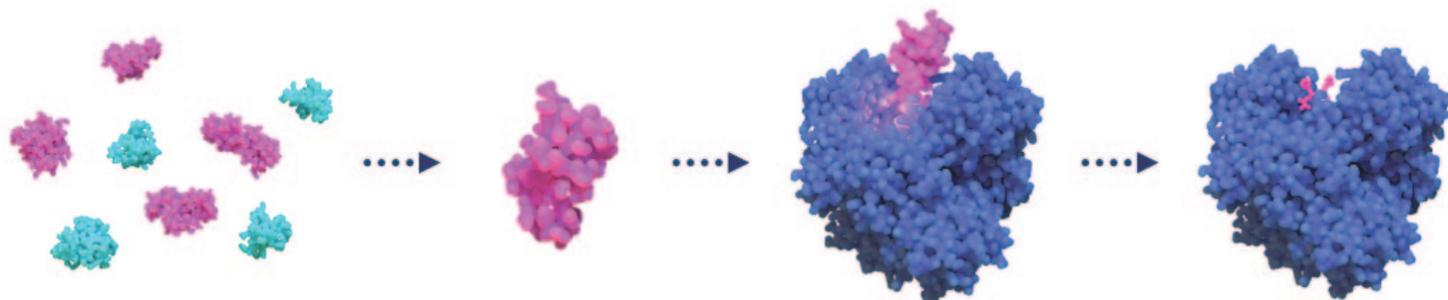
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# SUSTAINABILITY WITHOUT COMPROMISE



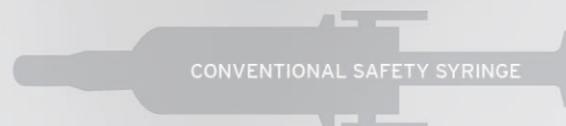
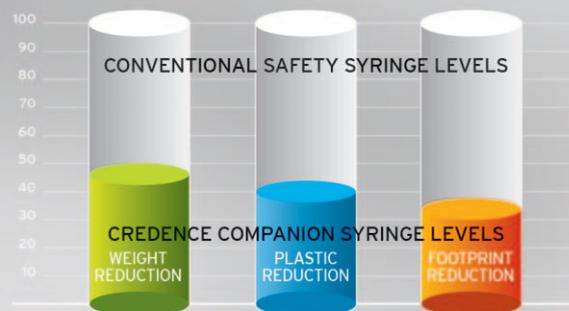
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## Wugen Secures \$115 Million to Advance Pivotal Study of First-in-Class Allogeneic CAR-T Therapy

Wugen, Inc. recently announced the closing of \$115 million equity financing led by Fidelity Management & Research Company, with participation from RiverVest Venture Partners, Lightchain Capital, Abingworth, ICG, LYZZ Capital, Tybourn Capital Management, Aisling Capital Management, and other leading life sciences investors. The proceeds will advance the ongoing pivotal T-RRex study of WU-CART-007 in relapsed/refractory T-cell acute lymphoblastic leukemia (T-ALL) and T-cell lymphoblastic lymphoma (T-LBL).

WU-CART-007, also known as soficabtagene geleucel, is a CD7-targeted, CRISPR-edited allogeneic CAR-T cell therapy with potential to be the first approved “off-the-shelf” CAR-T for T-cell malignancies. In a completed global Phase 1/2 study, WU-CART-007 achieved an overall response rate (ORR) of 91% and a composite complete remission (CRc) rate of 73% at the recommended Phase 2 dose. The median duration of response exceeded six months with manageable safety. These data, presented at the 2024 American Society of Hematology (ASH) Annual Meeting & Exposition, substantially surpass the outcomes achieved with current standard-of-care therapies.

“This financing comes at a decisive time for Wugen as we advance WU-CART-007 through our ongoing pivotal study with a clear path to a BLA filing in 2027,” said Kumar Srinivasan, PhD, MBA, President, and Chief Executive Officer of Wugen. “Relapsed and refractory T-ALL/T-LBL are aggressive malignancies resistant to current treatment options. We are committed to delivering an accessible, off-the-shelf therapy that can significantly improve the trajectory of patients’ care. We are grateful for the support of a world-class syndicate of investors who share our vision of transforming the treatment landscape for T-cell malignancies.”

Proceeds from this financing will fund the advancement of the pivotal T-RRex trial in patients with relapsed/refractory or minimal residual disease-positive T-ALL/T-LBL, regulatory engagement with the US FDA and European Medicines Agency (EMA), and preparations for commercial-scale manufacturing. The company anticipates a Biologics License Application (BLA) submission in 2027.

WU-CART-007 is an allogeneic, off-the-shelf, CD7-targeted CAR-T cell therapy engineered to overcome the technological challenges of harnessing CAR-T cells to treat T-cell cancers. Wugen is deploying CRISPR/Cas9 gene editing technology to delete CD7 and the T cell receptor alpha constant (TRAC) genes, thereby preventing CAR-T cell fratricide and mitigating the risk of graft-versus-host disease (GvHD). WU-CART-007 is manufactured using healthy donor-derived T cells to eliminate the risk of malignant cell contamination historically observed in the autologous CAR-T setting. WU-CART-007 is currently being evaluated in a global pivotal clinical trial for relapsed or refractory T-ALL/T-LBL. More information on the Phase 1/2 trial is available on [clinicaltrials.gov](https://clinicaltrials.gov), identifier NCT04984356 and on the pivotal trial on [clinicaltrials.gov](https://clinicaltrials.gov), identifier NCT06514794.

WU-CART-007 has received Regenerative Medicine Advanced Therapy (RMAT), Fast Track, Orphan Drug, and Rare Pediatric Disease designations from the U.S. Food and Drug Administration and Priority Medicines (PRIME) Scheme designation in the European Union for the treatment of relapsed or refractory T-ALL/T-LBL. RMAT and PRIME designations provide increased agency support to expedite the development and review of promising therapies for patients in need.

## TREOS Bio Partners With Charité Berlin & Junshi Biosciences to Launch Pivotal Phase 2 Clinical Trial in Refractory MSS Colorectal Cancer

TREOS Bio Ltd. recently announced the execution of clinical collaboration agreements with Charité – Universitätsmedizin Berlin and Junshi Biosciences for the initiation of OBERTO-202, a potentially registration-enabling Phase 2 clinical trial evaluating PolyPEP11018 in combination with toripalimab (Junshi Biosciences’ PD-1 inhibitor) and standard of care in microsatellite stable (MSS) metastatic colorectal cancer (CRC). The company also completed a \$2.1 million bridge financing from existing investors, bringing total financing raised to date to \$47 million, not counting non-dilutive support from grants and clinical collaborations.

The OBERTO-202 study will be conducted as an investigator-led trial at Charité – Universitätsmedizin Berlin, one of Europe’s largest university hospitals, with Prof. Sebastian Stintzing as principal investigator and in collaboration with 14 other leading academic hospitals. The trial will evaluate PolyPEP11018 and toripalimab in combination with standard of care (Lonsurf + Avastin) versus standard of care alone in approximately 140 patients with relapsed/refractory MSS CRC.

“The collaboration with Charité Berlin and Junshi Biosciences represents a significant milestone as we work toward demonstrating the potential of our precision immunotherapy approach in one of the largest oncology markets with significant unmet medical need,” said Dr. Christopher Gallen, Chairman and CEO of TREOS Bio. “The bridge financing provides us with the runway to advance our lead program toward what we anticipate will be a registration-enabling Phase 2 study.”

“This randomized, controlled clinical trial represents a logical next step in the development of PolyPEP11018,” said Dr. Hagop

Youssefian, Chair of Medical Strategy of TREOS Bio and Adjunct Professor of Medicine at Brown University. “Leveraging the built-in antigenic diversity of this unique active immunotherapy that can dampen multiple immunosuppressive mechanisms, in combination with toripalimab and chemotherapy, provides an exciting opportunity to overcome the well-known resistance to immunotherapies in MSS CRC.”

PolyPEP11018 is TREOS Bio’s lead off-the-shelf multi-peptide active cancer immunotherapy designed to convert immunologically “cold” tumors to “hot” tumors. The therapy has demonstrated encouraging clinical activity across three Phase 1/2 trials (44 patients in total) in advanced MSS CRC conducted in partnership with the Mayo Clinic, with consistent correlations between immune activation and clinical benefit.

MSS CRC represents approximately 85% of all colorectal cancer cases and affects an estimated 130,000 new patients annually in the US alone and over 1.6 million new patients globally. Current immunotherapies, including checkpoint inhibitors, have shown limited efficacy in this patient population.

TREOS Bio is a clinical-stage biotechnology company developing precision cancer immunotherapies based on its proprietary PASCAL (Personal Antigen Selection Calculator) platform. The company’s lead program, PolyPEP11018, is an off-the-shelf multi-peptide immunotherapy targeting shared tumor antigens with demonstrated clinical activity in MSS colorectal cancer. TREOS Bio has partnerships with leading institutions including Mayo Clinic, Charité – Universitätsmedizin Berlin, Roche and Junshi Biosciences. For more information, visit [www.treosbio.com](https://www.treosbio.com).

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## MannKind Announces Expansion of United Therapeutics Collaboration for Second Inhaled Therapy

MannKind Corporation recently announced United Therapeutics Corporation has exercised its option – granted under the companies' 2018 license and collaboration agreement – to develop a second dry powder inhalation therapy.

The original agreement, which led to US FDA approval of Tyvaso DPI in May 2022, included an option for United Therapeutics to expand the license to include additional active ingredients. Under the terms of the expanded agreement, MannKind will formulate a second investigational molecule using its proprietary Technosphere platform, and United Therapeutics will conduct pre-clinical and clinical development.

"Building on the success of Tyvaso DPI, we are proud to deepen our collaboration with United Therapeutics to bring innovative patient-centric inhaled therapies to patients living with pulmonary hypertension," said Michael Castagna, PharmD, Chief Executive Officer of MannKind Corporation. "This next step highlights the strength of our partnership and the versatility of our dry powder formulations and inhalation devices in addressing serious respiratory conditions."

Under the terms of the expanded agreement, MannKind will receive an upfront payment of \$5 million and is eligible to receive

up to \$35 million in development milestones and 10% royalties on net sales of any resulting product.

Formulation and development activities for the new investigational molecule will begin immediately.

MannKind Corporation focuses on the development and commercialization of innovative inhaled therapeutic products and devices to address serious unmet medical needs for those living with endocrine and orphan lung diseases. We are committed to using our formulation capabilities and device engineering prowess to lessen the burden of diseases such as diabetes, non-tuberculous mycobacterial (NTM) lung disease, pulmonary fibrosis, and pulmonary hypertension. Our signature technologies – dry-powder formulations and inhalation devices – offer rapid and convenient delivery of medicines to the deep lung where they can exert an effect locally or enter the systemic circulation, depending on the target indication. With a passionate team of Mannitarians collaborating nationwide, we are on a mission to give people control of their health and the freedom to live life. For more information, visit [mannkindcorp.com](http://mannkindcorp.com).

## Cereno Scientific Granted FDA Fast Track Designation for CS1 in Rare Disease Pulmonary Arterial Hypertension

Cereno Scientific recently announced the US FDA has granted Fast Track designation to its lead program, CS1, for the treatment of pulmonary arterial hypertension (PAH). Fast Track designation is designed to accelerate the development and regulatory review of new therapies for serious conditions with high unmet medical need. The designation highlights CS1's potential as a differentiated treatment approach for PAH, a rare and progressive disease where safer, disease-modifying therapies are urgently needed.

The FDA's Fast Track program is designed to facilitate the development and expedite the review of new drugs intended to treat serious conditions with the potential to address unmet medical needs. Fast Track designation enables closer and more frequent interaction with the FDA, eligibility for rolling review, and potential priority review, with the goal of bringing promising treatments to patients more quickly.

Drug candidate CS1 is an oral HDAC inhibitor (HDACi) with a unique mechanism of action through epigenetic modulation. In a Phase 2a trial in PAH, CS1 met its primary endpoint of safety and tolerability while showing encouraging efficacy signals in a Phase 2a trial in PAH, including improvement of REVEAL risk score, functional class, quality of life, and early signs of reverse vascular remodeling and improvement of right heart function. A global Phase 2b trial is being prepared to further evaluate CS1 as a potential disease-modifying treatment for PAH.

Cereno Scientific is pioneering treatments to enhance and extend life. The company's innovative pipeline offers disease-

modifying drug candidates to empower people suffering from rare cardiovascular and pulmonary diseases to live life to the full.

Lead candidate CS1 is an HDAC inhibitor that works through epigenetic modulation and represents a novel therapeutic approach by targeting the root mechanisms of the pulmonary arterial hypertension (PAH). CS1 is a well-tolerated oral therapy with a favorable safety profile that has shown encouraging efficacy signals of reverse vascular remodeling and improvement of right heart function as observed in a Phase 2a trial in patients with PAH. An Expanded Access Program enables patients that have completed the Phase 2a trial to gain access to CS1 CS014, a new chemical entity with disease-modifying potential, showed favorable safety and tolerability profile in a Phase 1 trial. CS014 is a HDAC inhibitor with a multimodal mechanism of action as an epigenetic modulator having the potential to address the underlying pathophysiology of rare cardiovascular and pulmonary diseases with high unmet needs such as idiopathic pulmonary fibrosis (IPF). Cereno Scientific is also pursuing a preclinical program with CS585, an oral, highly potent and selective prostacyclin (IP) receptor agonist that has demonstrated the potential to significantly improve disease mechanisms relevant to cardiovascular diseases. While CS585 has not yet been assigned a specific indication for clinical development, preclinical data indicates that it could potentially be used in indications like Thrombosis prevention without increased risk of bleeding and Pulmonary Hypertension.



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## Hongene to Supply exNA Oligonucleotide Technology Under New Licensing Deal

Hongene Biotech Corporation recently entered a non-exclusive licensing agreement with the UMass Chan Medical School to produce and supply extended nucleic acid (exNA) monomers and exNA-modified oligonucleotides for research use.

The agreement strengthens Hongene's RNA chemistry portfolio and expands access to innovative oligonucleotide technologies for academic and biopharmaceutical researchers developing RNA interference (RNAi), antisense oligonucleotides (ASOs), CRISPR guides, and other oligo-based modalities.

Developed by scientists at the RNA Therapeutics Institute at UMass Chan Medical School, exNA is a proprietary backbone modification that significantly enhances the durability and pharmacokinetics of oligonucleotide therapeutics, while maintaining compatibility with established small interfering RNA (siRNA) designs.

"This partnership reflects our strategy to bring next-generation RNA chemistries to market and support researchers working on the toughest delivery challenges in oligonucleotide therapeutics," said Dr. David Butler, Chief Technology Officer at Hongene. "By enabling access to exNA for research, we hope to accelerate

the development of RNA-based medicines for extrahepatic indications."

Under the terms of the agreement, Hongene will apply its expertise in phosphoramidite manufacturing and oligonucleotide synthesis to make exNA phosphoramidites and custom exNA oligonucleotides available through its catalog and bespoke services.

The expanded access to exNA technology is expected to help advance research into more stable, tissue-specific RNA therapeutics and support the development of novel medicines targeting areas of unmet clinical need. To learn more about Hongene's oligo CDMO services or discuss partnership opportunities, contact [info@hongene.com](mailto:info@hongene.com).

Hongene is a leading CDMO serving the global nucleic acid therapeutics industry. The company offers end-to-end support across oligonucleotide design, synthesis, analytics and scale-up, enabling clients to progress rapidly from discovery through commercialization.

## Vitalant & UPMC Expand Partnership to Advance Cell & Gene Therapy Initiatives

Vitalant is deepening its partnership with UPMC to support and enhance the health system's cell and gene therapy initiatives through medical leadership and laboratory operations. As part of this collaboration, Vitalant's Executive Medical Director for Biotherapies, Kevin Land, MD, is serving as the interim medical director for UPMC's Hematopoietic Stem Cell (HSC) lab. Playing a critical role in stem cell transplantation, the lab is recognized for its FACT, College of American Pathologists (CAP), and Clinical Laboratory Improvement Amendments (CLIA) accredited services.

Dr. Land will provide strategic medical oversight and guide the lab's evolution during this pivotal transition. His interim leadership will focus on strengthening clinical operations, aligning the lab's capabilities with emerging demands for cell and gene therapy, and laying the foundation for long-term growth. As part of this process, he will also lead a global search for a permanent medical director to ensure continuity and excellence in the lab's future direction.

"The HSC lab specializes in the collection, analysis, processing, and storage of human stem cells for potential therapeutic use in stem cell transplantation and is an integral part of the bone marrow transplant program," said Abbie Mallon, Vice President, UPMC Laboratory Service Center. "Expanding the UPMC and Vitalant partnership will allow us to continue to offer these important services while we think strategically about growth and innovation in this highly specialized field."

"This partnership underscores our collective dedication to advancing medical services and innovations in transplant and cell and gene therapy," said Becky Cap, Senior Vice president of Biotherapies for Vitalant. "Vitalant's clinical operations support aims to address both the clinical and logistical challenges in this innovative field."

"Vitalant is committed to supporting the advancements in cell and gene therapy, starting with hematopoietic stem cell transplants and extending to next-generation therapies," said Dr. Land.

"I'm thrilled to provide support on an interim basis, while partnering to identify the best medical leader for this role long-term."

This new physician position will also hold a part-time faculty position, collaborating closely with UPMC faculty and staff to ensure the growth and support of the lab's initiatives.

Vitalant and UPMC have a long history of partnering. Vitalant provides blood products, transfusion services, and coagulation testing to UPMC's main Pittsburgh campus and other locations across western Pennsylvania. Nationwide, Vitalant supports more than 900 hospital and healthcare organizations.

Vitalant is one of the nation's largest nonprofit blood and biotherapies healthcare organizations, providing hospitals and patients across the US a safe blood supply, specialized laboratory services, transfusion medicine expertise and world-renowned research. Vitalant's biotherapies program addresses a critical gap in the rapidly evolving cell and gene therapy landscape, bridging the space between patient needs and the current capabilities of the healthcare environment. We connect hospitals, therapeutic developers and patients, enabling the delivery of care to the communities where patients live.

UPMC is a world-renowned, nonprofit health care provider and insurer committed to delivering exceptional, people-centered care and community services. Headquartered in Pittsburgh and affiliated with the University of Pittsburgh Schools of the Health Sciences, UPMC is shaping the future of health through clinical and technological innovation, research, and education. Dedicated to advancing the well-being of our diverse communities, we provide nearly \$2 billion annually in community benefits, more than any other health system in Pennsylvania. Our 100,000 employees — including more than 5,000 physicians — care for patients across more than 40 hospitals and 800 outpatient sites in Pennsylvania, New York, and Maryland, as well as overseas. UPMC Insurance Services covers more than 4 million members, providing the highest-quality care at the most affordable price.

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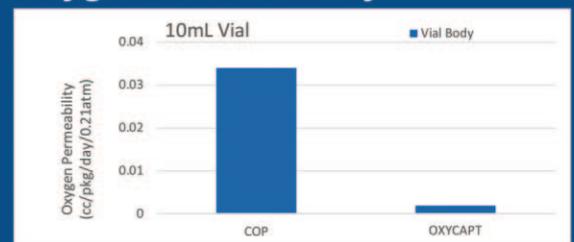
Water Vapor Barrier Layer (COP)

O<sub>2</sub> & CO<sub>2</sub> Barrier Layer (New Polymer)

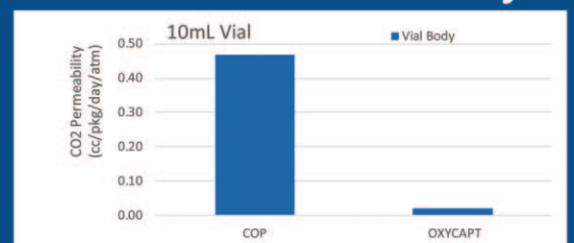
Drug Contact Layer (COP)

- **Excellent O<sub>2</sub> & CO<sub>2</sub> Barrier**
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- **Very Low Extractables**
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## Terumo to Acquire OrganOx Limited, a Leading Innovator in Organ Preservation Devices

Terumo Corporation recently announced it has entered into a definitive agreement dated August 3, 2025, with OrganOx Limited, a leading innovator in organ preservation devices, and its shareholders to acquire all outstanding shares of OrganOx. Upon completion of the transaction, OrganOx will become a wholly owned subsidiary of Terumo. The total transaction value is approximately \$1.5 billion.

The acquisition marks Terumo's strategic entry into the organ transplantation-related sector – a field with significant unmet medical needs and strong growth potential. By combining Terumo's longstanding expertise in designing medical devices and equipment with OrganOx's advanced capabilities in Normothermic Machine Perfusion (NMP), the Company aims to deliver innovative organ preservation devices globally. Terumo seeks to broaden access for patients in need of transplants and contribute to the advancement of transplantation medicine by aiming to address key challenges in organ transplantation, including improving organ utilization rates, enabling the use of marginal donor organs, enhancing post-transplant outcomes, and reducing the burden on healthcare professionals through minimizing nighttime and emergency procedures.

In the field of organ transplantation, a major challenge lies in the shortage of available organs relative to demand. Even in the United States, which performs the highest number of organ transplants, approximately 6,000 patients\*3 on the waiting list pass away each year without receiving a transplant. One of the key factors behind this shortage is the high rate of unused organs donated. Once organs are retrieved, they are promptly treated

and placed in organ preservation devices for transport to the recipient. However, if the organs are damaged during long-distance or prolonged transportation, the transplant may not be performed due to safety concerns. To reduce such missed opportunities, there is a strong need to establish new methods that enable long-term and stable preservation of donor organs.

Founded in 2008 as a spin-off from the University of Oxford, OrganOx is a pioneering medical technology company specializing in advanced NMP devices for organ preservation. NMP and other ex-vivo machine perfusion (EVMP) technologies can preserve organs longer by circulating oxygen and nutrient-rich perfusate through the organ at near-body temperature. In addition, NMP devices enable real-time monitoring of organ condition during storage and transport. This aims to help prevent the transplantation of organs with impaired function – with the goal of improving transplant success rates – as well as leading to a more effective use of organs from marginal donors.

OrganOx's liver NMP device, metra, received FDA approval in 2021 and was launched in the U.S. in 2022. The device has also obtained regulatory approvals in the EU, UK, Australia, and Canada, and is currently being commercialized in all of these regions. To date, the device has been used in over 6,000 liver transplant procedures worldwide. OrganOx has established itself as a leader in liver NMP technology and aims to achieve revenue growth that significantly outpaces overall industry expansion. In addition, OrganOx is currently developing a kidney NMP device, with commercialization targeted around 2030.

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# SUBCUTANEOUS INJECTIONS

## A New Dimension for an Enhanced Injection Experience

By: Enrico Barichello and Crystal Salvans

### INTRODUCTION

The global healthcare landscape is undergoing a significant transformation, driven by demographic shifts and evolving patient needs. As populations grow and age, the prevalence of chronic conditions is rising, necessitating long-term therapeutic strategies, usually administered through subcutaneous injections. However, the increasing demand for less-frequent dosing and patient-centric delivery methods is pushing the boundaries of current drug formulation and delivery systems.

To meet these expectations, pharmaceutical developers are exploring formulations that allow for reduced injection volumes or extended dosing intervals. These innovations, while beneficial for patient adherence and quality of life, often result in high-viscosity solutions that present significant challenges in terms of dose delivery. High viscosity solutions (eg, those above 30 cP) can compromise the ease and comfort of administration for patients with specific conditions, potentially impacting patient experience and treatment outcomes.

The following explores the impact of these market trends, focusing on the technical and clinical challenges associated with delivering large-volume, high-viscosity subcutaneous injections. It also highlights the need for optimized delivery systems that can accommodate these formulations without compromising usability or efficacy, as well as the potential advantages such systems may offer for non-viscous injections.

### MINIMIZING PATIENT PAIN DURING VISCOUS DRUG INJECTION

#### Theory of Needle Impact on Injection Forces

Injecting high-viscosity drugs using standard syringes can often lead to increased discomfort or pain for patients. The use of an 8-mm needle has been shown to help reduce this pain. In this section, we will explore how needle length can influence injection comfort, particularly in the context of high-viscosity formulations.

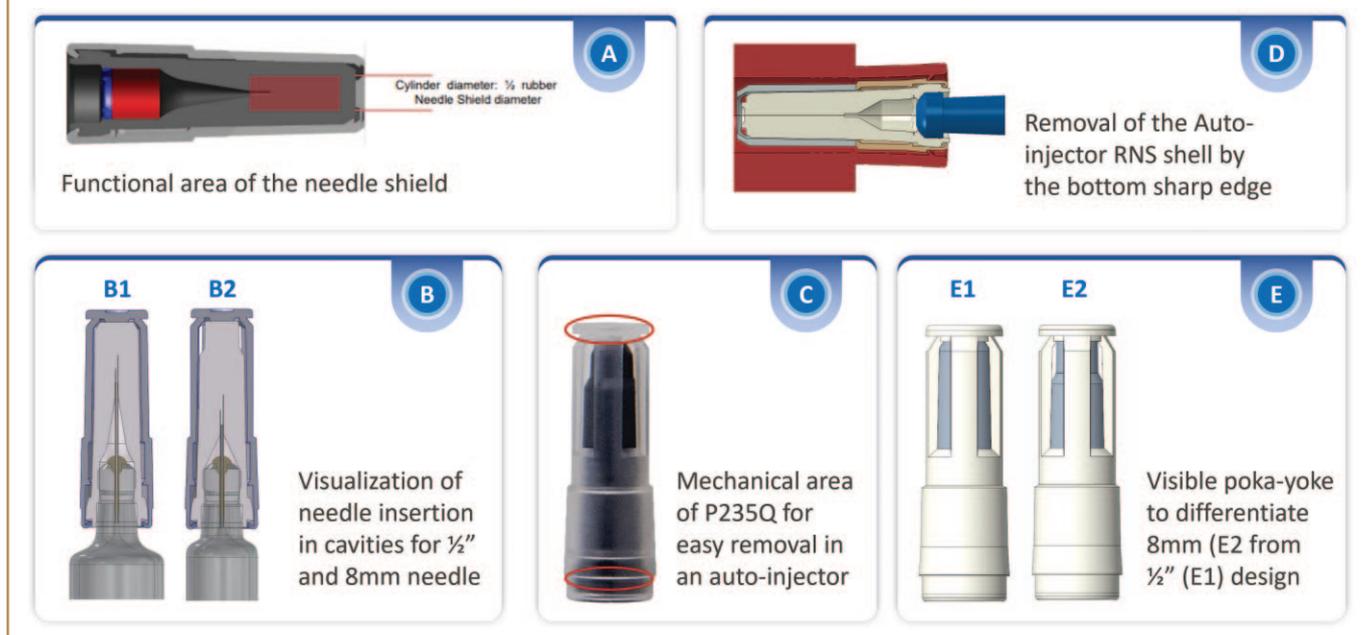
Multiple forces are exerted during the injection process. One of them is the hydrodynamic force.<sup>1</sup> The following equation determines the hydrodynamic force required for fluid injection:

$$F_{\text{Hydrodynamic}} = \frac{8\pi \cdot \mu_{\text{Liquid}} \cdot l_{\text{Needle}} \cdot r_{\text{Barrel}}^4}{r_{\text{Needle}}^4} \cdot \text{speed}$$

The force required to inject a fluid is directly proportional to the needle length ( $l_{\text{Needle}}$ ) and inversely proportional to the fourth power of the needle radius ( $r_{\text{Needle}}$ ). By reducing the exposed needle length to 8 mm and using a 27G Special Thin-Wall needle with an enlarged internal diameter, the design minimizes the hydrodynamic resistance. This results in lower injection forces, which not only improves the ease of administration, but also reduces the mechanical stress and discomfort experienced by the patient, thereby lowering the perception of pain.

Human factors studies conducted by Stevanato Group confirmed a clear preference for the 8mm STW needle, especially among both experienced and inexperienced self-injecting patients.<sup>2</sup> The strong positive feedback was driven not only by the reduced injection force, but also by the psychological benefit of

FIGURE 1



the shorter needle, which helped reduce anxiety and made the injection experience feel more manageable.

### Why do RNS Internal Cavities Need to be Adjusted According to the Length of the Needle?

The Rigid Needle Shield's (RNS) key functionality is to ensure the Container Closure Integrity (CCI), which is critical for preserving drug sterility, integrity, and patient safety. Two areas enabling it to maintain the CCI are represented in red in Figure 1A:

- Area 1: the cavity in contact with the tip of the syringe
- Area 2: the needle embedded in the rubber

The rubber component forms a tight, flexible seal around the needle and the syringe tip, blocking any potential pathways that could lead to microbial ingress or product degradation.

RNS are designed to help the needle insertion in the center of the cavity. Following needle insertion into the rubber core (Figure 1B), the seal remains effective,

thereby ensuring the product's sterility and safety up to the point of administration.

Therefore, with a lower needle length to support viscous product, having an RNS with adapted internal cavities is required to ensure an efficient seal.

### Integration Within the Auto-Injector System

Ensuring component compatibility with auto-injectors is essential to facilitate at-home medication and self-administration.

In this context, Alba® and Nexa® pre-fillable syringes have been specifically developed to enable reliable integration into auto-injector platforms. Both syringes feature tightly controlled dimensional tolerances and optimized barrel geometries to ensure consistent fit, secure assembly, and reproducible delivery performance within the device. Critical dimensional parameters, including the overall syringe length without closure (L1), the length above the shoulder (L2), and the total length including the rigid needle shield (L3) (Figure 2), have been precisely defined to support accurate injection depth, while also facilitat-

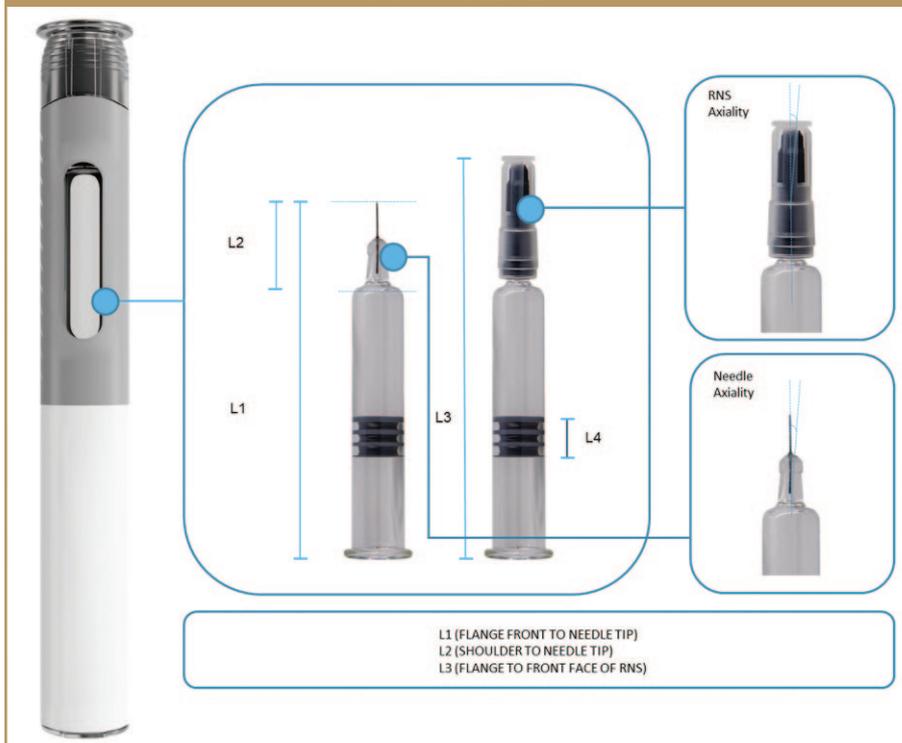
ing proper engagement during auto-injector assembly.

In addition, the axial alignment between the rigid needle shield and the syringe barrel is carefully controlled during manufacturing to ensure repeatable performance and compatibility across automated device assembly processes.

The 8mm RNS developed by Aptar Pharma integrates critical design and material to ensure optimal patented shell geometry, and the 4900GS rubber formulation enables a controlled Pull-Out Force (POF) while eliminating the risk of coring during needle insertion. This market-proven rubber formulation has been designed to ensure optimal compatibility with Biotech drug products.

To facilitate optimized integration with auto-injector systems, Aptar Pharma developed an innovative proprietary design that allows for efficient removal by gripping the top (enabled by a mushroom-shaped profile) or via a molded edge at the base (Figure 1,C&D). This dual-access approach enhances compatibility with various cap-removal mechanisms. Importantly, the RNS maintains the same folding

**FIGURE 2**



L1 (FLANGE FRONT TO NEEDLE TIP)  
 L2 (SHOULDER TO NEEDLE TIP)  
 L3 (FLANGE TO FRONT FACE OF RNS)

shell process as Aptar Pharma’s market-leading designs, which is instrumental in minimizing the risk of de-shielding.

Assessing the POF, which refers to the forces needed to remove the RNS from syringes, as well as the deshielding forces (DF) (meaning the forces required to separate the shell from the needle shield) is important. As auto-injector usage increases in the market, the variability and required POF values for compatibility with auto-injector mechanisms tend to be lower than those for stand-alone Pre-Filled Syringes (PFS). The two forces measured shouldn’t overlap to ensure product’s proper function.

As highlighted in Figure 3, with a safe margin area, POF and DF of the P235Q don’t overlap.

**How to Implement 8mm RNS & Syringe Without Impacting Machinability**

Processability on the customer filling line is a key parameter to be considered in any development. Therefore, the rubber

needle shield for the 8mm needle is combined with Aptar Pharma’s 0.5inch rigid shell for the auto-injector, and the syringe difference is only on the needle, meaning no external dimension variation, ensuring no modification of the customer’s filling line is required.

As a distinguishing feature in the filling line, the NS design incorporates a specific reduction in diameter at the top of the

needle shield, visible through the shell window (Figure 1,E). This feature provides a visible poka-yoke at every production stage, whether during RNS assembly, syringe assembly, or filling, ensuring that syringes with 0.5inch needles (E1) can be easily distinguished from those with 8mm needles (E2). As a result, the risk of mix-ups on filling lines is effectively prevented.

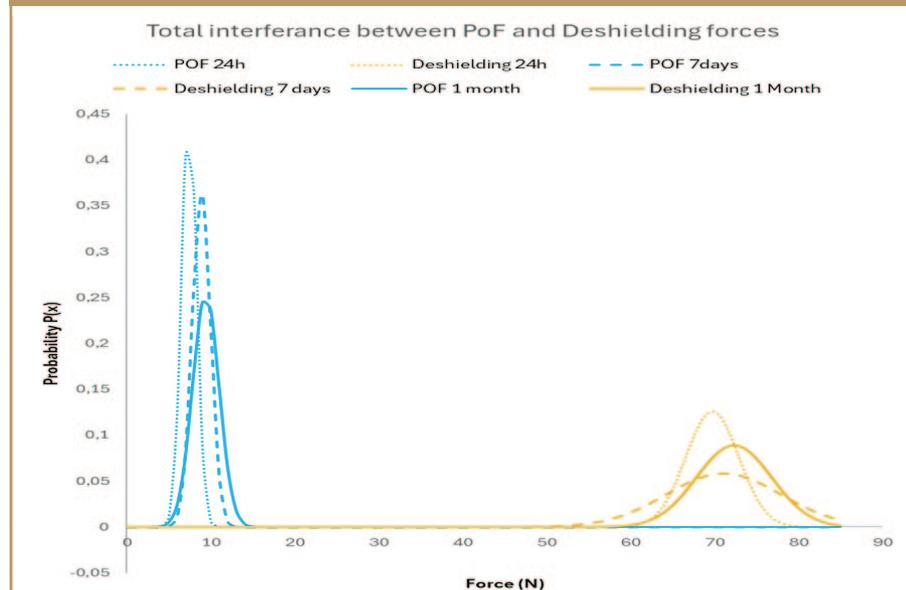
**PERFORMANCE ENHANCEMENT THROUGH THE PLUNGER & SYRINGE SYSTEM**

**Designing for Comfort: A Systemic View on Injection Force Management**

The Role of Plunger-Barrel Interface: The plunger and syringe’s main functions are to preserve container closure integrity (CCI), maintain drug stability, and facilitate drug delivery to the patient.

The efficacy of CCI and precise dose administration is contingent upon an optimal interference fit between the plunger and barrel, facilitating adequate compression and sealing. This interface induces friction during injection, dictated by parameters such as applied force, friction co-

**FIGURE 3**



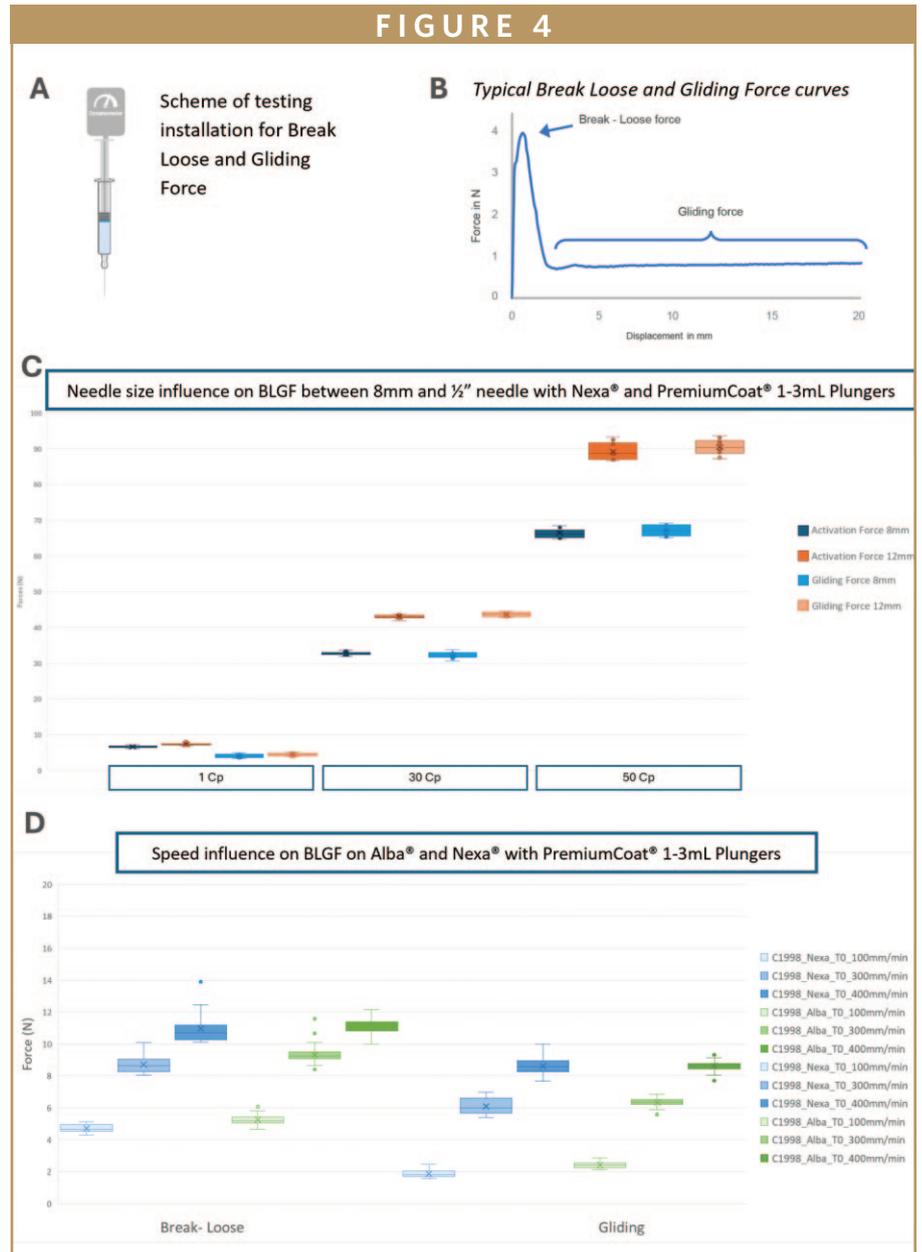
efficient, rubber-glass interfacial adhesion, viscoelastic hysteresis of the elastomer, effective contact area, surface roughness, and the extent of lubrication or siliconization.

The break-loose (BL) force, required to initiate plunger movement, and gliding forces (GF), needed to sustain movement, are crucial for successful injections. They determine the ease-of-use of a PFS and its integration into an auto-injector.

### Stevanato Group's Alba® Syringe, Featuring a Proprietary Cross-Linked Coating:

To enable proper movement within the system, both the glass barrel and the rubber stopper typically require lubrication with silicone oil. In the Alba® platform, a proprietary cross-linked silicone coating is applied to the inner barrel surface, creating a stabilized, low-migration lubricant layer. This immobilized coating is designed to maintain drug stability over time (even in the presence of aggressive surfactants often used in highly concentrated biologics), while ensuring consistently low and predictable glide forces. Such performance is particularly critical in auto-injector applications, where reliable break-loose and glide forces are essential to ensure that even low-force springs can successfully deliver the full dose to the patient.

**Aptar Pharma's PremiumCoat®:** For decades, Aptar Pharma offers a large range of plungers designed to be compatible with syringe and devices and using ultrapure formulations. To address the most sensitive drugs, Aptar Pharma launched in 2021 PremiumCoat plungers platform, combining an ETFE film coating, which is applied at the drug contact surface, with our single, pure formulation 6720 and its



state-of-the-art innovative manufacturing process. The following introduces how PremiumCoat combined with Nexa® and Alba® syringes can address the challenges of injecting large viscous drugs.

As previously detailed, current trends aim at reducing dosing frequency for patients and increasing the viscosity of the solutions delivered.

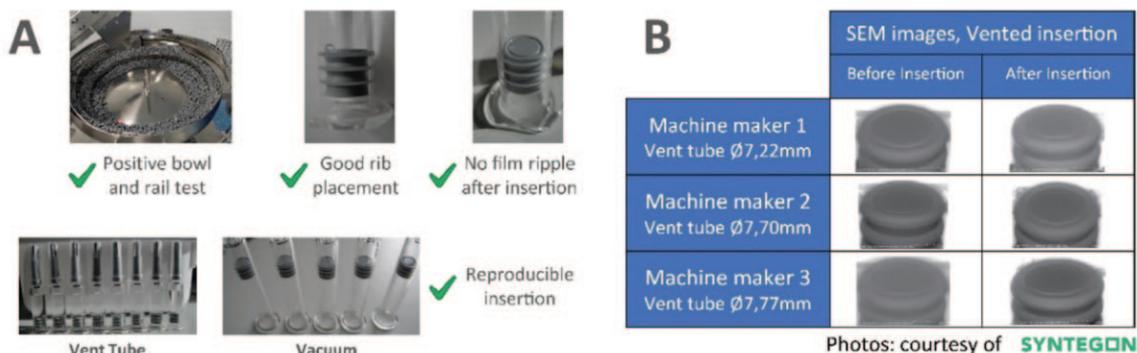
### Performance Testing With Viscous Drugs

Using a dynamometer, technical experts assessed the BLGF of PremiumCoat® 1-3mL plungers in combination with

Alba® and Nexa® syringes filled with water-like fluid and fluids of various viscosities. Each measurement yields a graph of forces, which indicates the BL and average GF (Figure 4, A-D). First, the speed was fixed at 300 mm/min, and the solution had various viscosities (1 - 30 - 50 Cps), comparing the results of a Nexa® syringe when it has a 0.5inch 27G TW and 8mm 27 Special Thin Wall needle pushed by an Aptar PremiumCoat 1-3mL plunger.

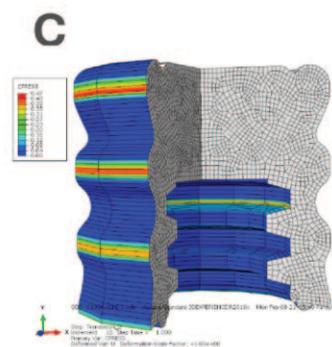
Second, the test was conducted with an Alba® and Nexa® syringe filled with water (1Cp) solution at various speeds to assess the speed impact in AI. Comparing

FIGURE 5



**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 tubes diameters. Photo courtesy of Syntegon.
- C. Compression area of Aptar PremiumCoat® 1-3mL with ISO nominal syringes barrel



BLGF in a system of Nexa® syringe and Aptar Pharma’s PremiumCoat® 1-3mL plungers with an 8mm STW or ½” TW needle, there is little difference for non-viscous liquids. However, with viscous drugs (30 or 50 Cps), both forces decrease by 25% when using the 8mm STW needle.

The speed of injection can vary and is a critical parameter in auto-injector performance. The faster an injection is done, the higher the speed will be. When using the Alba® syringe (featuring a cross-linked silicone coating) in combination with the PremiumCoat® 1-3mL, the system demonstrates improved consistency and reduced variability, particularly at higher injection speed. These results are driven by

the combination of a stabilized, immobilized silicone layer on the syringe barrel and the proprietary 3-rib design of the PremiumCoat plunger. The 3 ribs maintain continuous contact with the barrel, ensuring constant pressure distribution with glass and therefore enabling smooth forces during the injection phase (Figure 5C).

**How do the Functional Properties of PremiumCoat Facilitate Integration in Filling Lines?**

Plungers were tested with both vacuum and vent-tube stoppering machines, which are known for altering ETFE films in other coated plungers. In both methods,

Aptar Pharma’s film-coated plunger demonstrated a great machinability compatibility by maintaining its film integrity. For more details, read our article published on October 21 in Drug Development & Delivery titled Exploring How the Functional Properties of the PremiumCoat 1-3-mL Plunger Facilitate its Implementation on Filling Lines & Enable the Delivery of Sensitive Vaccines & Biotech Drugs.<sup>3</sup>

**SUMMARY**

In summary, driving innovation in injection systems demands a collaborative and patient-centric approach that unites

pharmaceutical developers, device manufacturers, and technology partners. By keeping the patient at the center of each decision, we can achieve solutions that not only optimize system performance, but genuinely enhance patient experience and safety. Aptar Pharma's advanced Rigid Needle Shield, Premium-Coat® Plunger, and its integration expertise (strengthened by a fruitful collaboration with Stevanato Group) stand as a testament to our commitment in supporting the evolving needs of the biotech industry. By leveraging our proven know-how and cutting-edge products, we support our partners to navigate the complex landscape of high-viscosity and novel drug formulations, accelerating and derisking drug development, while ultimately improving outcomes and quality of life for patients. ♦

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## BIOGRAPHIES



**Enrico Barichello** is Product Manager for the Syringe Platform at Stevanato Group. He earned a Master's degree in Industrial Engineering from the University of Padua. Since joining Stevanato Group in 2017, he has worked closely with cross-functional teams to define and execute the roadmap for new products, including the Alba® platform. Since 2023, he has overseen the glass syringe platform, and as of January 2025,

also manages the polymer syringe platform, driving innovation and growth across Stevanato Group's syringe portfolio.



**Crystal Salvans** is the Product Line Manager for PFS at Aptar Pharma's Injectables division. She earned an Engineering degree in Packaging from ESIREIMS and began her career as a Packaging Engineer at Johnson & Johnson (now Kenvue), before joining Aptar Pharma Injectables in 2015. With expertise in injectables packaging, she has held roles in Technical Support, Project Management, and Sterile Gamma Irradiation,

managing a Technical Product Management team. Currently, she leads a team managing the project and product life cycles for plungers, RNS, and tip cap components.



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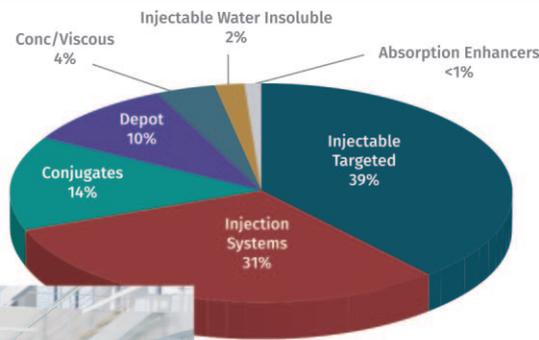
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Excipient vs Strength	
	375 mg telaprevir
HYPROMELLOSE ACETATE SUCCINATE 12070923 (3 MM2/S) (Core/Content)	375 mg
SODIUM LAURYL SULPHATE (Core/Content)	7.58 mg
DIBASIC CALCIUM PHOSPHATE ANHYDROUS (Core/Content)	75.76 mg
CROSCARMELLOSE SODIUM (Core/Content)	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)	

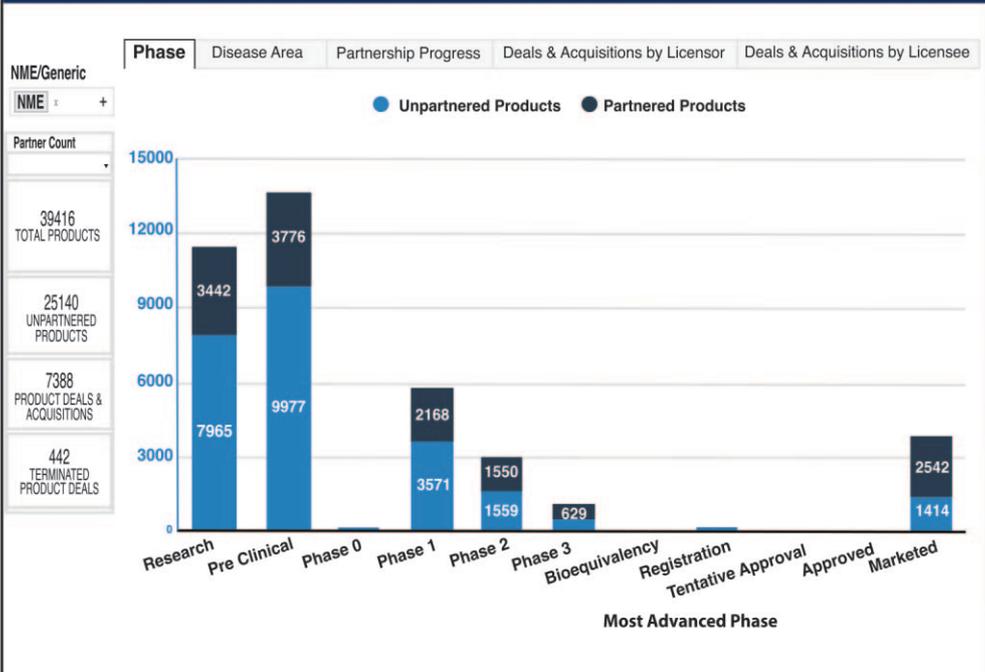


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# FORMULATION FORUM

## Hot Melt Extrusion – An Enabling Technology for Poorly Soluble Drugs

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**KEYWORDS:** Hot melt extrusion, amorphous solid dispersion, polymers, extrusion temperature, ASD, polymer screening, drug-polymer miscibility, solubility, supersaturation, bioavailability, glass transition temperature, AmorSol®, NanoSol®

### INTRODUCTION

Since the original use of hot melt extrusion (HME) in the plastics industry in the mid-19th century, this technique has gained significant traction in the pharmaceutical field in the recent past. There is a tremendous interest in using hot melt technology to address the challenges in formulating molecules as solid amorphous dispersions (ASDs) for improving solubility and oral bioavailability.<sup>1</sup> It is critical because a majority of the BCS II and IV molecules are poorly water soluble and/or permeable, so conventional solubilization technologies, such as micronization, pH modification, and complexation, may not help achieve the desired supersaturation solubility in a typical dosage, especially medium-to-high drug-loading formulations.<sup>2</sup>

Among the ASD technologies, HME and spray drying (SD) are commonly used. As opposed to spray drying, HME is a solvent-free process; therefore, it is highly preferred, though finding the appropriate polymers compatible to drugs and higher temperatures could be challenging for crystalline, high melting (brick dust), and lipophilic molecules with high log P.<sup>3</sup> In spite of these challenges, drug manufactures continue to look for

TABLE 1

Brand Rx	Drug	Company	Year	Polymer	Indication
Alvaiz®	Eltrombopag	Teva	2023	PVPVA	Blood product & modifiers
Belsomra®	Suvorexant	Merck	2014	PVPVA	Sleep disorder
Braftovi®	Encorafenib	Pfizer	2018	PVPVA	Antineoplastic
Kaletra®	Lopinavir/Ritonavir	Abbvie	2000	PVPVA	Antiviral
Lynparza®	Olaparib	Astra Zeneca	2017	PVPVA	Antineoplastic
Mavyret®	Glecaprevir/Pibrentasvir (in tablets & pellets)	Abbvie	2017/2021	PVPVA	Antiviral
Norvir®	Ritonavir	Abbvie	2018	PVPVA	Antiviral
Noxafil®	Posaconazole (tablets & powder for oral suspension)	Merck	2013/2021	HPMCAS	Antifungal
Paxlovid®	Nirmatrelvir/Ivacaftor	Pfizer	2023	PVPVA	Antiviral
Qulipta®	Atogepant	Abbvie	2021	PVPVA	Antimigraine
Technivie®	Ombitasvir/Paritaprevir/Ritonavir	Abbvie	2015	PVPVA	Antiviral
Ubrelvy®	Ubrogepant	Abbvie	2019	PVPVA	Antimigraine
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Viekira® PAK & XR	Dasabuvir & Ombitasvir/Paritaprevir/Ritonavir	Abbvie	2014/2016	PVPVA	Antiviral

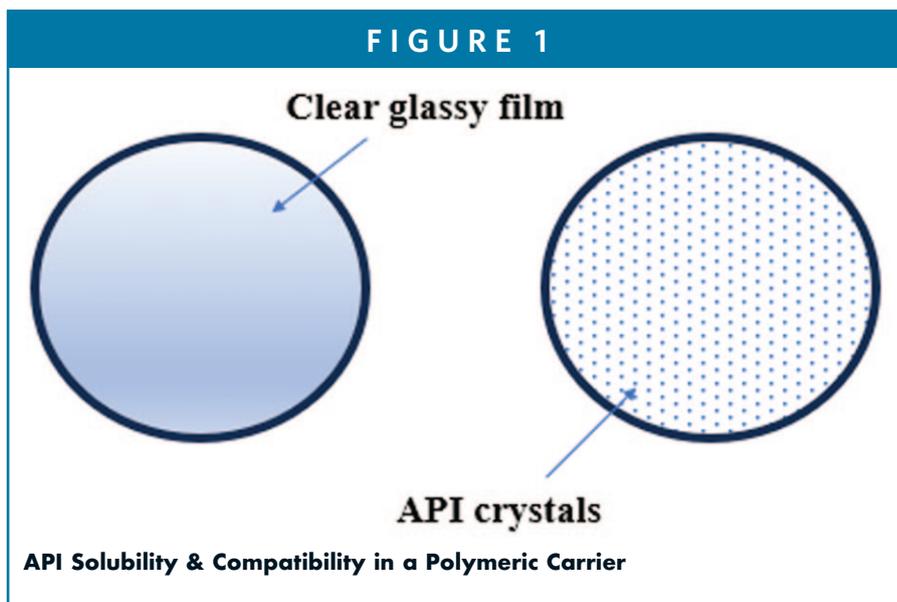
Several HME Drugs Approved by the FDA<sup>5</sup>

non-conventional, and often novel, polymers to expedite the development of innovative molecules coming out of discovery when none of the conventional technologies do not meet the desired objectives.<sup>4</sup> The following will focus primarily on HME of solid oral dosage forms.

In the recent past, over 20 drugs using HME technology have been launched, as shown in Table 1.<sup>5</sup> Citing a few, for example, Kaletra® (lopinavir/ritonavir) in tablet, was the first approved HIV drug that comprises copovidone and uses Span 20 as a solubilizer and plasticizer for the melt extrusion. The process further involves calendaring that leads to compression of granules into tablets in the downstream process. It was the first major breakthrough to reduce pill burden to avoid dose variabilities in fed and fasted states and to improve room temperature stability over that of Kaletra in soft gel capsules.<sup>6</sup> This solubilization technology is also applicable to diverse dosage forms, including taste-masking of bitter drugs, controlled/sustained release, targeted drug delivery, and nanoparticles.<sup>7</sup>

## SCREENING OF POLYMERS FOR HME

Figure 1 illustrates the drug miscibility and immiscibility in polymeric carriers. A clear glassy film (as solid solution) suggests the drug is soluble in the polymer, whereas the precipitation in the polymer film suggests the drug is insoluble at and above those concentrations used. Briefly, for low-to-medium throughput screening, drug and polymers are dissolved in polar solvent(s) as a clear solution, which is used to cast films on a glass plate. The solvent is removed under nitrogen and/or by placing the plate in an oven at 50°C for an extended period. This process allows the polymer to challenge with different drug concentrations. Higher drug concentrations in a polymer may lead to



nucleation or precipitation, indicating the polymer is not compatible with higher drug loadings. With APIs having a plasticizing effect, higher drug loading leads to higher miscibility in the polymers as a solid solution. The ideal miscibility of drug in polymer leads to one combined  $T_g$ , which lies in between  $T_g$  (determined by DSC) of polymer and that of amorphous drug, depending upon their concentrations in the binary mixtures.<sup>8</sup>

Solubility parameters of polymers and drugs are used to predict the miscibility of drug into polymers. Hansen solubility parameter, for example, is calculated by computer program SPWin (version 2.1) by the individual contributions of dispersive components, polar components, and hydrogen bonding components, as shown in Equation 1.<sup>9</sup>

$$\delta_{\text{total}} = \sqrt{\delta_d^2 + \delta_p^2 + \delta_h^2}$$

Where,  $\delta_d$  is dispersion force,  $\delta_p$  is dipole to dipole force, and  $\delta_h$  is hydrogen bond. The total solubility parameter is calculated as under root of all three parameters combined. For example,  $\delta$  (total) value for Soluplus® is 19.4 MPa<sup>0.5</sup>, and for Copovidone (Kollidon® VA64), it is 19.7 MPa<sup>0.5</sup>.

Similarly, for drugs like Fenofibrate,  $\delta$

(total) value is 21.4 MPa<sup>0.5</sup>, and for itraconazole, it is 22.6 MPa<sup>0.5</sup>. If  $\Delta\delta$  between drug and polymer is <7 MPa<sup>0.5</sup>, drug might be miscible, but this difference may not predict to what extent of drug is soluble in the polymer. Therefore, to fully access the miscibility in the polymers during screening, it is important to evaluate the range of drug solubility in the polymers by challenging with different drug concentrations.<sup>10</sup>

## POLYMERS FOR HME

Polymers play a crucial role in dissolving the drug in the matrices. The higher the molecular weight of polymers provides better and stronger entanglement with drug molecules via H-bonding and van der Waal's interactions, making them more stable as opposed to short polymeric chains.<sup>9</sup> Thus, the stability of drug in long-chained polymers is significantly greater than short-chain polymers. Thus, it is important to assess the stability in selected polymers in pre-formulation that meets the desired critical quality attributes (CQAs). Therefore, for HME formulations, identifying an ideal polymer is crucial. First, the polymer is thermally stable and interacts with drug to preserve the amorphous state of the

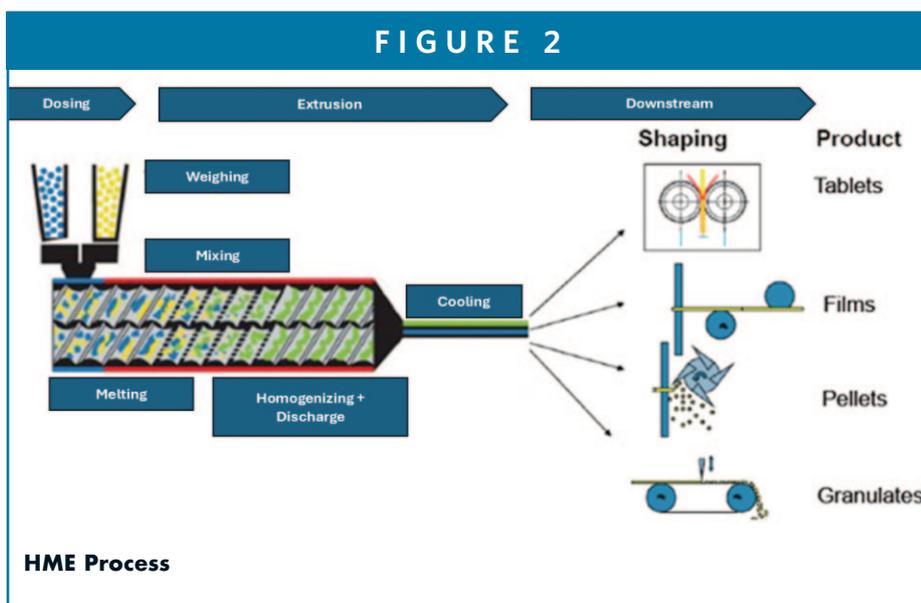
drug for an extended period during manufacture and storage. It should also be hydrophilic and able to dissolve easily under GI pHs.

Commonly used excipients for solid dispersions include the following:<sup>7</sup>

- PVP: Polyvinylpyrrolidone (K12, K17, K25, K-30, K-90)
- Copovidone: Vinylpyrrolidone - vinyl acetate copolymer
- Soluplus- PEG-co-PVAc-co-PVCap
- Kollicoat IR: PEG-co-PVA
- Hydroxypropyl methylcellulose (Hypromellose): HPMC
- Hydroxypropyl cellulose: HPC
- HPMC acetate succinate: HPMC-AS
- HPMC phthalate: HPMC-P
- Polyethylene oxide: PEO (MW > 20K) or PEG (MW < 20K), PEG/PPG
- Methacrylic or acrylic copolymers: Kollicoat MAE 100 P, Eudragit® EPO, L100-55
- Kollidon® SR – PVP/PVAc (co-processed)

## HOT MELT EXTRUSION (HME) PROCESS

Figure 2 shows the schematic diagram of an extrusion process. It involves several steps for achieving the solid solution: (1) mixing of drug in polymeric carrier in molten state under controlled temperature, (2) extrusion at a specific temperature and die pressure, screw speed, and configuration, (3) cooling off the extrudates, and (4) cutting of extrudate in tablets, films, pellets or granules.<sup>11</sup>



The extrusion temperature of drug is typically kept at least 50°C above the glass transition temperature ( $T_g$ ) of polymer. In many cases, despite a higher melting temperature of crystalline drugs, molten polymer may act as a solvent to help dissolve the API without reaching its melting point. This entire process enables the dispersion of drug within the carrier as an amorphous state or meta-stable states. In cases where the  $T_g$  of polymers are too high, the extrusion process is tackled by adding the plasticizers by lowering the extrusion temperature of polymer. The higher the  $T_g$  of polymers, the higher the impact of plasticizers have and vice versa.<sup>9</sup>

Briefly, HME is an efficient, solvent-free, continuous manufacturing method for converting crystalline drugs into an amorphous state. In molten state, polymers act as solvents and as thermal binders that hold back drug release upon cooling and solidification. In a single screw extruder, the screw rotates inside the barrel and is used for feeding, melting, devolatilizing, and pumping. It is good for initial screening of drugs in a range of polymers. The twin screw extruders offer a better option with the choice of different configurations to obtain better mixing and extrusion by allowing

temperature zones in the barrel exposed to different thermal conditions from transfer of material from the hopper to the screw, all the way to the metered pumping zone and exit through die at the end. Twin-screw extruders have advantages over single screw extruders in terms of easier material feeding, high kneading and dispersing capacities, less tendency to over-heat, and shorter transit time.<sup>12</sup> Equipped with corotating screws or counter-rotating screws, these extruders are used for various pharma applications. The counter-rotating twin-screw extruders are not preferred as they lead to potential air entrapment, high-pressure generation, and low maximum screw speeds and output. Thus, the co-rotating twin screw extruders are most preferably used for pharma applications.

## APPLICATION OF HOT MELT EXTRUSION (HME)

The following also sheds some light on the application of HME for pharma dosage forms.

## Immediate Release of Solid Oral

### Dosages

HME has been used in formulating brick dust molecules with the intent for immediate delivery of drugs. Therefore, polymer selection is the very first step to identify appropriate hydrophilic polymers with higher molecular weight that enables them to interact effectively with drug molecules through intermolecular bonding. Copovidone, Povidone, Soluplus, pH dependent enteric polymers, among others, are typically preferred to effectively extrude with and without plasticizers, depending upon their  $T_g$ . The extrudates in the downstream process are cut into pellets/granules and filled in hard gel capsules or blended and mixed with diluents as fillers, binders, glidants, and lubricants before compressing in tablets. The tablets prepared by compression are typically large (over 1 g) with a polymer/drug ratio of 90:10 or 80:20 with the exceptions of higher drug loading to 30%-40% wt%. For example, 10% of 17-estradiol was extruded with 50% PVP and 40% Glucire® 44/14 showed an immediate release with 32-fold increase in dissolution rate.<sup>13</sup> Sun et al. evaluated nimodipine by HME in a formulation composed of Eudragit L100 and Plasdone S630 and filled in HMPC hard gel capsules with PEG400 and PEG 6000 as auxiliary excipients, and achieved similar bioavailability as the reference drug in beagle dogs.<sup>14</sup> The use of PEGs helped prevent the recrystallization of drug in the matrix, further demonstrating choice of excipients makes remarkable difference of the stability and performance of drugs.

### Sustained & Delayed Release of Drugs

The selection of polymers with inherent hydrophobicity plays an important role in controlled release of drugs. HME extrusion might require use of plasticizers to help extrude the drugs, especially with higher drug amounts. Brabender et al. evaluated in healthy

volunteers ibuprofen extruded in cellulosic excipients with xanthan gum as controlled-release matrix and found that  $C_{max}$  and AUC were significantly lower than commercially available Ibu-slow® tablets. In another study, Zhang and McGinity evaluated chlorpheniramine maleate (CPM) at 20% in high molecular weight PEO as a carrier with PEG3350 as plasticizer and found that the drug was stable, and drug-release properties were not affected by drug loading at 20% or higher.<sup>15</sup> Darji et al evaluated Kollicoat MAE 100 for delayed release of ibuprofen using melt extrusion. The extruded pellets when subjected to dissolution studies showed 1.5% release at pH 2 in 2 hours, whereas a complete release in the next 2 hours at pH 6.8, suggesting using an HME, the enteric properties of Kollicoat MAE100 is maintained, thus, alleviating the possibility for tablet coating.<sup>16</sup> Drug loading in the extruded pellets ranged 40%-50%. Meltrex® technology has been used for controlled release HME products.<sup>17</sup>

### Implants for IM, SC & Ocular Drug Delivery

HME has been used for delivery of drugs via intramuscular, subcutaneous, and intraocular routes of administrations. The formulation and delivery of drugs depends for such applications on polymer characteristics, such as their hydrophilicity and hydrophobicity, compositions, degradation behavior, molecular weight, crystallinity and amorphous nature, and hygroscopicity, among other attributes. Polymers, including PLGA, PLA, PGA, polyurethane polyanhydrides, and polyesters, among others, are commonly used in HME, due to biodegradability in nature. In a study, Stankovic et al. used amorphous block copolymers composed of PCL-PEG/PCL for extrusion of lysozyme at 55°C, which showed an extended release over 180 days.<sup>18</sup> In another study, Li et al. demonstrated PLA/PEG-

polypropylene glycol-PEG copolymer extruded with dexamethasone showed controlled release over an extended period.<sup>19</sup> Likewise, polyesters have been used in HME for a controlled-release formulation of bovine serum albumin.<sup>20</sup> Ozurdex®, an intravitreal implant composed of dexamethasone extruded with PLGA, was approved in 2009 for treatment of macular edema and noninfectious uveitis. Zoladex® is a subcutaneous implant composed of goserelin acetate in PLGA and has been approved for sustained release of drug over 12 weeks. Other examples include Implanon™, a subcutaneous implant composed of etonogestrel in EVA for controlled release of drug over 3 years.<sup>21</sup>

## SUMMARY & FUTURE PERSPECTIVES

As new molecules continue to be investigated and remain challenging due to their poor solubility and bioavailability, the pharma industry is exploring all viable options to expedite the development for bringing drugs to market faster. HME offers a platform for solid dosage as well as other dosages like IM/SC implants. As a solvent-free process, this technique can lead to seamless continuous process in upstream and downstream for small and large molecules and is compatible for a wide range of synthetic and natural polymers and excipients and solubilizers. With the advent of newer equipment with higher throughput and smaller footprints, HME can lead to better and efficient continuous manufacturing processes, thus making it more attractive for immediate-release and controlled-release applications. HME can also be used in injection molding, 3D printing, co-extrusion, melt granulation, and formation of co-crystals.

Ascendia offers several solubilization platforms for challenging molecules. With its

enabling technology platform, AmorSol®, Ascendia can help to expedite the discovery and development of drugs by converting crystalline drug into stable ASDs. Other enabling technologies, like NanoSol® are applicable to nanosuspensions could be used as depots, an alternative to melt extruded implants. ♦

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# PULMONARY DELIVERY

## Development of Pulmonary Dosage Forms for the Successful Delivery of Complex Molecules

By: Richard Johnson, PhD

### INTRODUCTION

The administration of drugs into the lung is a well-established delivery route for the treatment of a wide range of pulmonary ailments. The direct delivery of drugs to the respiratory system is ideal for the localized treatment of chronic lung diseases, such as asthma, chronic obstructive pulmonary disease (COPD), pulmonary hypertension (PA), and a number of drugs used in the treatment of chronic lung conditions associated with Cystic Fibrosis.

These lung treatments traditionally relied on devices, such as metered dose inhalers (MDIs) and nebulizers, to deliver drugs to where they were needed in the lung. In many cases, these devices delivered drugs in the upper airways of the lung as well further down the lung architecture.

Whilst these chronic lung conditions will remain a high priority in pulmonary delivery, there is growing interest in delivering drugs deep into the alveolar space for treatments of diseases within the lung or for subsequent systemic delivery after the drug has crossed the lung epithelium.

TABLE 1

Device Type	Mode of Action	Advantages	Challenges/Limitations
<b>Metered Dose Inhalers</b>	A non-aqueous propellant fires the drug dose out of the device into the throat, lung	-Portability, convenient to use, non-breath-actuated delivery. -Low cost of manufacture	-Requires proper coordination of breathing/dosing -Many biologics are not compatible with propellants -Serious environmental concerns over propellants used
<b>Nebulizers</b>	Provides a continuous “drug mist” via a face mask that is inhaled by the patient (typically over several minutes)	Preferred for pediatrics and geriatrics (no need to coordinate with breathing)	-Significant proportion of the dose does not reach the target -Expensive device -Cleaning required -Aggressive atomization can be damaging to biologics
<b>Soft Mist Inhalers</b>	Hand-held devices that deliver a fine, aqueous mist (containing the drug) into the deep lung	-Ease of use (compared to nebulizer) -Gentle atomization -High fraction of fine particles for deep lung delivery	-Coordinate breath with delivery of the dose -Requires drug to be solubilized in aqueous media
<b>Dry Powder Inhalers</b>	Patient inhalation to draw powder out of the device into the lung	-Potential to deliver high doses into the deep lung -Dry powders offer improved stability for thermally sensitive drugs (biologics)	-Cost of manufacture -Moisture sensitivity of the dry powders may cause problems -Requires inhalation energy to get the drug out of the device into the deep lung

Advantages & Challenges With Pulmonary Device Types

**FIGURE 1**



**Buchi B-290 Bench Top Spray Dryer**

Traditional devices, such as MDIs and nebulizers, are less suited for many of these next-generation drug treatments as: (1) both types of devices result in significant quantities of the delivered dose being deposited in the throat and upper airways of the lung, reducing efficacy and causing side effects and (2) many of these drugs

are sensitive biologics or oligonucleotides that have limited stability in water or are not compatible with the propellants used in MDIs.

Because of these challenges, there is growing interest in next-generation pulmonary delivery devices that can overcome either or both of these challenges, ie, delivering drugs more efficiently into the deep lung and also delivering thermally sensitive drugs that are unstable in solution. These next-generation delivery devices include soft mist inhalers (SMIs) and dry powder inhalers (DPIs). Some of the advantage/disadvantages of these pulmonary delivery devices are summarized in Table 1.

### DEVELOPING DRY POWDER & SOFT MIST INHALER DOSAGE FORMS

There is growing interest in delivering drugs into the deep lung for localized treatments or for subsequent systemic uptake.

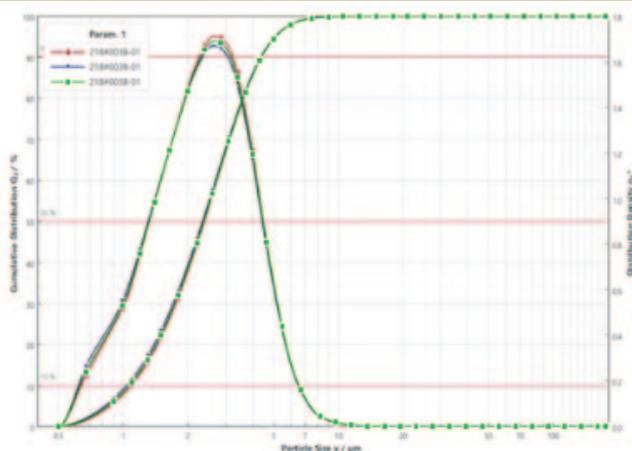
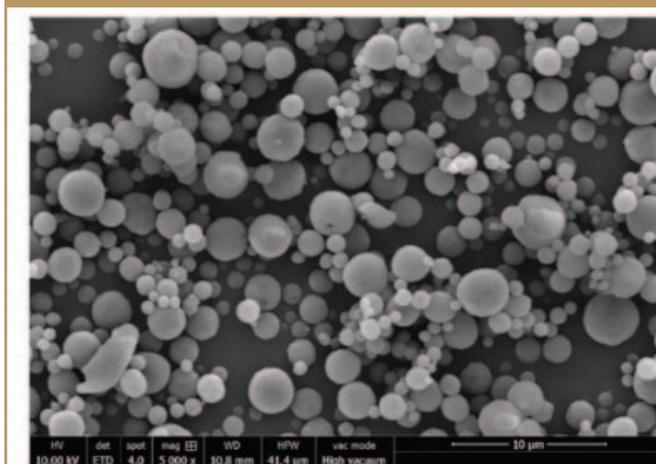
When developing a DPI or an SMI formulation containing the drug of choice, it is important to remember the performance of the pulmonary dosage form will be dependent on the properties of the formulation itself (powder or liquid) in combination with the device used to deliver the dose.

Clearly, the development pathway for either dosage form differs in many ways as one type of device requires a dry powder and the other an aqueous liquid. However, both types of dosage forms have factors in common, namely the need to assure accurate dosing, a high degree of deep lung deposition (fine particle fraction), and a suitable stability profile.

### Developing Dry Powder Inhaler Dosage Forms Containing Biologics

The successful development of DPI dosage forms require the creation of a dry powder formulation of the drug that has the correct aerodynamic size for deep lung delivery. Typically, this requires creating drug/excipient formulations with a particle size of around 1  $\mu\text{m}$  to 3  $\mu\text{m}$ . The best technique for creating or “engineering”

**FIGURE 2**



X <sub>10</sub>	X <sub>50</sub>	X <sub>90</sub>	VMD
1.35	2.79	3.07	3.07

**Electron Micrograph & Sympatec Particle Size Analysis of a Spray-Dried Pulmonary Dosage Form**

**TABLE 2**

Excipient Type	Function
<b>Polyols (eg, mannitol)</b>	Crystalline carrier that can be used to create crystalline drug complexes
<b>Sugars (eg, disaccharides such as trehalose, sucrose)</b>	Used to create solid particles that are amorphous in nature, increasing stability of complex biologics
<b>Surfactants (eg, polysorbate 80, DSPC)</b>	Can protect sensitive molecules during the spray-drying process (polysorbate 80). Can also be used to encapsulate drugs (DSPC) to improve bioavailability and help overcome barriers such as the mucociliary lung clearance
<b>Amino Acids (eg, leucine, glycine)</b>	Perform a range of functions such as pH control and surface coating (eg, leucine) to improve aerodynamic performance

**Common Excipients Used in Dry Powder Pulmonary Dosage Forms**

these drug/excipient particles is spray drying.

Spray drying is particularly useful as the drying equipment comes in a range of sizes that can produce small batches of powder (milligrams), such as the Buchi B-290 spray dryer (Figure 1) through to much larger GEA-Niro spray dryers that can produce batch sizes of hundreds of kilograms, with established tech transfer models and scale up models.

In early development studies drug/excipient solutions can be prepared and spray dried to create particles with the required aerodynamic size for deep lung delivery. Typically, when creating dry powder formulations containing complex biologics (such as peptides, proteins, oligonucleotides, vaccines), it is necessary to add excipients that perform a range of functions. Some of the key excipients and their functions are summarized in Table 2.

A typical development program will involve mixing one or more of these excip-

ients in solution with the drug in a ration that can achieve the target loading needed for an efficacious dose. These solutions can then be spray dried using conditions that can typically create fine particles in the size range suitable for deep lung delivery (respirable fraction).

Typical size distributions and particle morphologies that can be produced by spray drying are shown in Figure 2.

Once powders have been produced, it is important to test the powders to see if they have the required physical and chem-

ical attributes for successful pulmonary delivery.

Stability of the drug (especially biologics) is essential, and retaining stability is required during the spray drying process (ie, ensuring activity and structure of the biologic remains the same as before spray drying) and on subsequent storage over time.

**Developing Soft Mist Inhaler Dosage Forms Containing Biologics**

Developing liquid formulations that can be delivered using an SMI is much simpler compared to developing a dry powder version. The biologic in question is typically dissolved in an aqueous buffer solution (typically around neutral pH) at a concentration that will allow the required dose to be delivered.

A typical dose delivered from an SMI is typically between 10  $\mu$ l to 30  $\mu$ l, so depending on solubility of the biologic, the actual dose delivered in a single actuation is relatively low (typically  $\mu$ g quantities compared to a DPI which can deliver several milligrams per dose). Examples of typical excipients that can be added are summarized in Table 3.

When pilot formulations have been produced, it is important to test the solutions to see if they have the required physical and chemical attributes for successful

**FIGURE 3**



**Copley NGI Fitted With a Dry Powder Device Ready for Aerodynamic Particle Sizing**

pulmonary delivery via an SMI. These include stability of the drug in the liquid (bulk) solution and the delivery performance from the device itself.

## TESTING DELIVERY PERFORMANCE & STORAGE STABILITY OF DPI & SMI DOSAGE FORMS

Two key steps in the successful development of a pulmonary drug dosage form (delivered by a DPI or an SMI) are: testing that the required dose can be delivered from the device and that it can reach the deep lung (the fine particle fraction), and ensuring the dosage form remains stable at its intended storage conditions. In many aspects, the testing of these two critical parameters is similar for both devices.

### Measuring Aerodynamic Particle/Droplet Size & Determining Fine Particle Fraction in DPI & SMI Dosage Forms

The Fine Particle Fraction (FPF) is often defined as the fraction or percentage of the drug mass contained in an aerosol or powder that is small enough to enter the deep lung and exert a clinical effect.

Geometric sizing can be used to measure the size of the particles or droplets that come out of either device. For example, Figure 2 shows a typical laser particle size distribution from a pulmonary formulation produced by spray drying.

However, the FPF of the dose can only be measured when it has been delivered by the device in question and its aerodynamic deposition pattern has been determined.

To measure the FPF requires the use of a multi-stage cascade impactor, such as

the Next Generation Impactor (NGI) manufactured by Copley Instruments (Figure 3).

A DPI or an SMI containing the drug dose can be fired into the Copley NGI and the drug deposition at each stage determined, typically using an HPLC method or by simple UV absorbance.

The Copley software can then be used

to measure the Fine Particle Mass (or FPF) generated by the formulation/device combination. A typical FPF for a spray-dried dosage form delivered by a Plastiapi DPI can be seen in Figure 4.

### Determining Storage Stability in DPI & SMI Dosage Forms

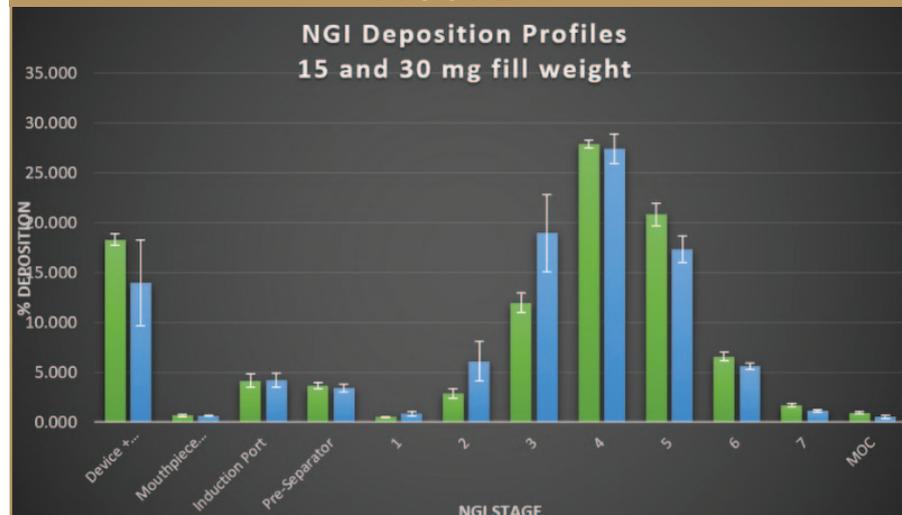
A critical aspect in the successful de-

TABLE 3

Excipient Type	Function
Buffers (eg, phosphate, histidine)	Maintain a stable pH of the solution for stability and reducing irritancy on dosing
Tonicity agents (eg, NaCl)	Ensure that the solution is isotonic, avoiding irritancy
Surfactants (eg, polysorbate 80)	Can protect sensitive molecules during the spray generation process
Preservative (eg, benzalkonium chloride, EDTA)	To inhibit bacterial growth during storage
Solvents (eg, ethanol)	Reducing aerodynamic droplet size by creating smaller droplets

Common Excipients Used in SMI Dosage Forms

FIGURE 4



NGI Data Generated From a Spray-Dried Dosage Form Delivered by a Plastiapi DPI

TABLE 4

Analytical Test	Stability Attribute	DPI	SMI
HPLC Analysis (assay & related substances)	Drug substance remains intact	Y	Y
NGI Impactor Testing	Measure aerodynamic particle/droplet size from device	Y	Y
Delivered Dose	Dose delivered from the device remains constant	Y	Y
Tonicity	Confirm isotonicity is maintained	N	Y
pH	Confirm pH is maintained	N	Y
Microbiology	Ensure the delivered dose	Y	Y
Moisture	Ensure no moisture is entering the device	Y	N
Preservative Assay (HPLC)	Preservative remains intact	N	Y

**Typical Analytical Tests Used to Assess Storage Stability of DPI or SMI Dosage Forms During Dosage Form Development**

velopment of a DPI or an SMI pulmonary dosage form is that of storage stability, ie, ensuring the formulated drug remains stable when filled into the device at the desired storage conditions.

Typically, filled devices will be stored at a range of temperatures/humidities, and at predefined time periods, devices will be withdrawn from storage and the dosage form subjected to a range of analytical tests. Typical stability indicating assays are shown below in Table 4.

lenging class of molecules. Each of these devices has advantages and disadvantages, so choosing between them should be done on a case-by-case basis.

The subsequent development and testing of DPI and SMI dosage forms can be challenging, but many of the techniques used are compatible with either dosage form, and the end result remains the same for both - the successful delivery of a suitable dose into the deep lung from a stable formulation/device combination. ♦

## SUMMARY

The pulmonary delivery route is of increasing interest to those looking to deliver more complex molecules, such as biologics, into the lung for local or potentially systemic delivery.

Whilst there are a number of device options available to deliver drugs into the lung, DPIs and SMIs are the two most widely used device types for the more chal-

## BIOGRAPHY



**Dr. Richard Johnson** is the Founding Director and Chief Scientific Officer of Upperton Pharma Solutions, a UK-based Contract, Development and Manufacturing Organisation. Graduating from Warwick University with a PhD in Biochemistry, he was employed as a Protein Chemist at Delta Biotechnology. In 1994, he was part of a management buy-out team that founded Andaris Ltd, a research and development company exploiting the use of spray-drying technology in the fields of diagnostic imaging and drug delivery. In 1999, he founded Upperton and has overseen significant growth and expansion over the past 25 years.

# Drug Development EXECUTIVE



Kim Shepard

Director, Advanced  
Drug Delivery

Lonza



Carsten Rudolph, PhD

Co-founder & CEO

Ethris



## Lonza & Ethris: Advancing mRNA Vaccines: Room-Temperature Stable, Spray-Dried Formulations for Enhanced Mucosal Delivery

mRNA vaccines have rapidly grown in popularity due to their industrial adaptability, responsiveness to new variants, and shorter development timelines. Current market research predicts the mRNA vaccine market to be valued at \$18.28 billion by 2030. Despite this growth, challenges associated with developing mRNA vaccines remain, including dependence on ultra-low-temperature storage and complex delivery systems.

To tackle these challenges, Lonza, one of the world's largest contract development and manufacturing organizations (CDMOs) and Ethris, a clinical-stage biotechnology company pioneering next-generation RNA therapeutics and vaccines, recently announced a collaboration to develop room-temperature stable, spray-dried formulations of mRNA-based vaccine candidates, designed for mucosal delivery that offer a promising approach to combat respiratory diseases.

*Drug Development & Delivery* recently interviewed Kim Shepard, Director of Advanced Drug Delivery at Lonza, and Carsten Rudolph, PhD, Co-founder and Chief Executive Officer at Ethris, to discuss the main objectives of the collaboration and the benefits of spray-dried mRNA vaccines.

## Q: What is the main goal of the collaboration between Ethris and Lonza?

**Dr. Rudolph:** Our collaboration with Lonza is part of our broader strategy to develop first-in-class spray-dried mucosal mRNA vaccine candidates that are stable at room temperature and capable of generating a localized immune response, funded by the Coalition for Epidemic Preparedness Innovations (CEPI). The initial focus of the collaboration is to develop a candidate against influenza. By generating a localized immune response at the site where the virus enters the body, we aim to potentially reduce virus transmission and enhance vaccine efficacy, while minimizing systemic exposure. On the other hand, the development of vaccine formulations that remain stable at room temperature addresses significant supply chain issues related to the need for ultra-low-temperature storage for certain mRNA vaccines. Achieving this stability can streamline the production process and lower costs, thereby making vaccine distribution more efficient and scalable.

**Ms. Shepard:** Our team at Lonza Bend is excited to collaborate with Ethris on their vaccine candidates to target unmet medical needs in the field of non-invasive vaccine delivery. The spray-dried formulations are designed for needle-free administration, which can enhance patient compliance and accessibility. While our collaboration is focused on creating a first-in-class mRNA vaccine candidate against influenza, we look forward to the possibility of expanding to other respiratory diseases in the future.

## Q: How does spray-drying technology enhance the stability and delivery of mRNA-based vaccines?

**Ms. Shepard:** Spray-drying technology significantly improves the stability and delivery of mRNA-based vaccines by transforming liquid formulations into a dry powder. This is essential because the dry powder form is more stable at room temperature, unlike liquid formulations that often need ultra-low temperature storage and rely on a complex supply chain. This stability at higher temperatures helps to address the logistical challenges related to cold chain requirements, making mRNA vaccines more accessible and easier to distribute.

Additionally, the dry powder form of mRNA vaccines provides versatility in delivery methods. Spray drying as a technique enables particle engineering, allowing the material to be designed for delivery to the lung or nose via inhalation. This flexibility allows for targeted delivery to specific areas of the body

where mucosal immunity can be induced, enhancing the vaccine's efficacy by ensuring that the immune response is generated at the site of virus entry.

## Q: What are the challenges in producing spray-dried mRNA vaccines?

**Ms. Shepard:** mRNA vaccines are usually formulated within lipid nanoparticles (LNPs), which can present challenges when creating spray-dried mRNA vaccines. This is primarily related to the stability and integrity of the mRNA and the need for effective encapsulation within LNPs. Consequently, the manufacturing process must be meticulously controlled to ensure the production of consistent and high-quality vaccine particles.

For instance, the size of the LNPs must remain consistent to facilitate effective transfection into cells. Effective delivery to the respiratory tract also requires particles with a median size of at least 20  $\mu\text{m}$ , while minimizing the presence of fine particles that could reach the lungs.

**Dr. Rudolph:** A primary challenge pertains to the mechanical stress induced during spray drying that can cause aggregation of LNPs in standard formulations. The drying process additionally exposes the formulation to significant heat, damaging most formulations.

As such, it is important to select the excipients carefully to ensure stability. The matrix excipient plays a key role in preventing the aggregation of LNPs during the drying process while maintaining the integrity and activity of the mRNA. Furthermore, it must ensure consistent physical stability and preserve the particle's morphology during storage. Common matrix excipients include sugar alcohols, polysaccharides, and certain polymers. For respiratory delivery, additional excipients may be added to enhance the aerosol properties of the powder, thereby improving emission from an inhaler device.

Ethris has pioneered a series of proprietary innovations, such as the inclusion of a stabilizing excipient that completely prevents LNP aggregation. Additionally, Ethris' technology allows formulations to remain stable at temperatures from  $-20^{\circ}\text{C}$  up to room temperature and at elevated temperatures. These innovations protect the LNPs from heat damage and aggregation – two common failure points in standard formulations – and ensures particle integrity during nebulization and spray-drying.

By further tailoring our proprietary SNaP LNP<sup>®</sup> formulation for spray-drying, Ethris enables Lonza to efficiently apply spray-drying and particle engineering. We provide robust, shear-

resistant, and thermostable LNPs to facilitate the spray-drying process, resulting in optimal mRNA encapsulation, particle size, mRNA concentration, excipient composition, and LNP integrity with preserved bioactivity and enhanced physical stability.

#### **Q: What are the benefits of nasal administration of mRNA vaccines over traditional intramuscular injections?**

**Dr. Rudolph:** Nasal administration of mRNA vaccines offers distinct advantages over traditional intramuscular (IM) injections, primarily by inducing robust immunity at the mucosal surface of the respiratory tract - the main entry point for respiratory viruses like SARS-CoV-2 and influenza. Unlike IM vaccines, which mainly generate systemic immunity (IgG antibodies in the bloodstream), studies show that nasal vaccines can rapidly induce both mucosal and systemic immunity, by eliciting strong local production of immunoglobulin A (IgA) and tissue resident memory B and T cells within the nasal and airway mucosa. This dual response forms an effective barrier, intercepting pathogens at the site of entry, and is particularly effective in halting viral shedding and breaking the cycle of person-to-person transmission, something IM vaccines struggle to achieve due to their weaker mucosal response.

Additionally, through targeted delivery of mRNA vaccine, we have shown that we minimize systemic exposure. Our recently finalized Phase 1 study of our nasal formulation demonstrated no systemic bioavailability of the mRNA or expressed protein product.

Another advantage of nasal vaccination is that it is completely needle-free, making it much easier for patients to self-administer. This may improve patient compliance and facilitate mass vaccination campaigns.

Combined with the benefits of room-temperature-stable mRNA formulations, which ensure easy storage and distribution, mucosally delivered mRNA-vaccines are a promising tool for protecting vulnerable patient populations, controlling respiratory pandemics, and reducing disease spread at the community level.

#### **Q: What are the benefits of enhanced stability of spray-dried formulations and how does Lonza contribute to the development of these formulations for mRNA vaccines?**

**Ms. Shepard:** As a contract development and manufacturing organization (CDMO), Lonza brings a wide array of expertise to

the development of spray-dried mRNA vaccine formulations. One of the strongest areas of expertise we have is related to advanced particle engineering, particularly mastering the spray drying process to create powder particles with precisely controlled properties essential for stability and delivery.

This is complemented by our extensive experience handling sensitive biologics, which is especially helpful in selecting the appropriate excipients to protect the delicate mRNA molecules and their lipid nanoparticle (LNP) carriers from degradation during the drying process and throughout the product's shelf-life.

Our sites in Geleen, Netherlands, and Visp, Switzerland, offer integrated mRNA and LNP capabilities. These sites have dedicated process development, analytical services, and cGMP manufacturing for clinical trials. Complementing these capabilities, our team provides end-to-end support in bringing these complex formulations from the laboratory to large-scale production. This involves robust process development and meticulous scale-up under stringent Good Manufacturing Practice (GMP) conditions, ensuring consistency and quality.

#### **Q: How does Ethris' Stabilized Non-Immunogenic mRNA (SNIM RNA) and Stabilized NanoParticle (SNaP) LNP platform facilitate the creation of room-temperature stable vaccine formulations?**

**Dr. Rudolph:** At Ethris, we have created a proprietary lipid formulation with a unique composition and stabilization mix that ensures excellent mRNA stability at temperatures ranging from -20°C to room temperature. This innovation is complemented by our development of lyophilization and rapid rehydration processes, which provide long-term product stability and enable room temperature storage and distribution.

Moreover, we have introduced a stabilizing excipient that can be added to the LNP formulation to completely prevent LNP aggregation caused by mechanical stress, such as shaking during vaccine distribution. Additionally, we are advancing the development of a spray-dried formulation, which not only offers long-term storage but also represents an easily scalable process. ♦

# SPECIAL FEATURE

## Injection Devices: Faster, Integrated & Flexible for the IV to SC Transition

By: Cindy H. Dubin, Contributor

The global injectable drug delivery market was valued at \$633.77 billion in 2024, currently stands around \$690 billion, and is forecast to reach \$1.03 trillion by 2030.<sup>1</sup> Use of wearable injectors, autoinjectors, and needle-free systems is being driven by the rising prevalence of chronic diseases, an increasing demand for biologics, and patient preference for self-administration. Additionally, the move towards personalized medicine and combination therapies has spurred more tailored and smarter delivery solutions for complex drug regimens.<sup>1</sup>

According to the World Health Organization, diabetes, cardiovascular diseases, and cancer account for more than 74% of all deaths annually, highlighting the need for injectable drug delivery technologies. Infectious diseases are also increasing, driving demand for injectable delivery.<sup>1</sup>

“The future of injectable delivery is incredibly promising, particularly as we see rapid advances in combination product design, device technology, and patient engagement tools,” says Dawn Manley, Director Global Technical Sales at PCI Pharma Services. “From a development standpoint, I’m particularly excited about the growing alignment between formulation science and device engineering, which will allow for faster, more integrated development pathways and greater flexibility in delivering therapies that improve lives globally.” Additionally, industry experts see a need for more flexible and expanded design that enables complex subcutaneous drug delivery.



**Precision in hand – cartriQ® 5mL from SCHOTT Pharma.**

This annual, exclusive *Drug Development & Delivery* magazine report highlights how device developers are addressing these challenges while still ensuring precise dosage control and patient compliance.

## Artcraft Health: A Transfer of Knowledge Ensures Safe & Accurate Self Injections

Did you ever get a new TV and couldn't get the remote to work? It looked like your last remote so you assumed it would work the same, but it didn't. Now, imagine a busy nurse practitioner about to train a patient on how to use an on-body injector that looks like the one she's used hundreds of times. After a few tries, she can't get the new device to function properly, and that means lost time and patients put at risk.

"Ironically, it may be injection-experienced clinicians who make more errors than patients when adopting new or retooled devices," says Marty Mason, Senior Director, Demo and Training Devices at Artcraft Health, a full-service health education company. "Whether due to muscle memory or ingrained expertise, it's not uncommon for an HCP to wrongly predict that a new device should work the same as a previous one." This tendency, known as negative transfer, can lead to errors and incorrect dosing. While some experienced patients may also make negative transfer errors, "injection-naïve" (first-time) users may be more cautious and make fewer errors.

Says Todd Zimmermann, Managing Director of Artcraft, "We've learned from our deep experience in patient education and human factors studies that when a demo device accurately mimics an actual device through seamless reverse engineer-



ing, error-free training is possible. We aim to match the commercial experience as closely as possible for a smooth transition from training to real use. That's why we developed demoX™, an electromechanical device with built-in sensors that replicate the physical, visual, and auditory cues of an injection device."

Mason notes that the demoX autoinjector, which delivers five times as many demo cycles as traditional mechanical demo devices, can be adapted for on-body injectors as well. He says that Artcraft Health is well-versed in on-body device training, having engineered and produced thousands of demo device kits as part of a client's global training initiative for a combination therapy that uses on-body injectors. As biosimilar and new drugs emerge for similar indications that use on-body injectors, the risk of negative transfer increases because patch injectors look similar, but may have different functionality. For example, clinicians may incorrectly attempt to bottom fill a device that now fills from the top, since they're used to a previous delivery method.

"Our solution to mitigate negative transfer is to educate users right from the

beginning using a cross-platform approach that successfully transfers their knowledge from one device to another," says Stephanie Murrin, Chief Creative Officer, Artcraft Health. "For example, we would create a demoX on-body training device in tandem with our customizable eLearning training system, checkEd™, to capture all the features and nuances of a device. That way we can facilitate successful onboarding by HCPs and help patients feel confident self-administering their drugs from the start."

## BD: Partnering to Bring Complex Molecules to Market

One of the biggest challenges in injectable delivery from BD's perspective is balancing drug formulation requirements with available device solutions to deliver high-dose biologics. High-dose formulations can have a high viscosity profile (30 centipoise or more) or higher volume dose (greater than 2mL) or even both. These types of formulations can be challenging to deliver subcutaneously with device component options developed for use within a narrower design space. Because many of

the new biologic drugs in the pharma development pipeline, as well as commercially approved biologic drugs, being transitioned from intravenous (IV) to subcutaneous (SC) delivery are in high-dose formulations, BD sees this challenge continuing if not growing, going forward.

“Based on that, we see pharma seeking components that expand the design space for subcutaneous delivery of high-dose biologics while leveraging existing infrastructure in the pharma ecosystem,” says Beth McBride DiLauri, Director of Global Marketing, BD Medical – Pharmaceutical Systems.

BD is actively collaborating within the pharma ecosystem to offer multiple options for pharma to increase flexibility as they develop high-dose drugs in drug-device combination products. These device collaborations enable pharma flexibility within an expanded design space for high-dose biologics while leveraging existing infrastructure for fill, finish and final assembly.

First, BD is partnering with autoinjector companies such as SHL and Ypsomed to enable handheld delivery of viscous biologics using an autoinjector within the traditional injection time constraint of ≤15-20 seconds. These collaborations are focused on allowing a wider design space for higher viscosity drugs by enabling compatibility of BD Neopak™ XtraFlow™ Glass Prefillable Syringe with commercially available autoinjectors. Studies of these configurations have demonstrated reduced injection time while using BD Neopak XtraFlow syringe with their commercially available autoinjectors, when compared to syringes with 27G thin-walled, 1/2-inch needle, says Ms. McBride DiLauri.

Second, BD is integrating its larger volume delivery solution, BD Libertas™ Wearable Injector, into the pharma supply chain infrastructure for drug-device combination products. BD is currently collaborating with multiple Contract Manufacturing Organizations (CMOs) to establish fill, finish, and final assembly options within pharma’s supply chain network. In addition to the BD-sponsored clinical trial completed with BD Libertas Wearable Injector that was published in 2020, which successfully demonstrated the ability to deliver 5mL drug volume with BD Libertas wearable Injector, BD is also enabling pharma’s evaluation of a complex biologic in a pharma-sponsored clinical trial with BD Libertas Wearable Injector. “These collaborations demonstrate another approach BD is taking to support pharma in delivering high-dose biologics to the market,” she says.

### Credence MedSystems, Inc.: Supporting Shortened 5mL Barrels for 3mL Dosing

The growing shift toward biologics and long-acting injectables has created strong demand for subcutaneous (SC) delivery of larger volumes, approaching the 3mL to 5mL range. While SC injections were once limited to 1mL, developers now seek devices that can extend this boundary without compromising patient comfort, manufacturability, or safety. One practical

approach is the use of cut-down 5mL barrels to deliver 3mL volumes, allowing existing filling lines to be used without costly retooling, while avoiding the handling and injection challenges associated with longer syringe barrel geometries.

“The Credence MedSystems Companion® Syringe System offers advantages to address the challenges created by this trend,” says John A. Merhige, Chief Commercial Officer, Credence MedSystems, Inc. “Unlike traditional exoskeleton-based devices, which require an entirely new platform for each barrel size, the Companion integrates its safety and usability features directly into the syringe. By keeping the safety technology integral, the Companion platform applies seamlessly across 1mL, 2.25mL, 3mL, and 5mL syringe barrels – including shortened 5mL barrels used for 3mL delivery. This consistency reduces development risk, simplifies supply chains, and ensures a uniform user experience across a drug portfolio. In contrast, exoskeleton approaches add bulk, drive operational inefficiency, and often intimidate patients with their unfriendly handling and appearance – creating hurdles for both manufacturers and end users.”

Patient comfort and adherence remain critical considerations with higher SC volumes. The Companion system supports user-controlled injection, minimizing the impact of force variability and enabling more tolerable delivery of viscous formulations. Its automatic needle retraction and



**The Credence Companion® in a '3mL Short' Configuration.**

passive safety features protect patients and caregivers alike, while maintaining the familiar handling of a prefilled syringe. “For therapies transitioning from infusion to SC injection, this combination of safety and familiarity is essential to adoption,” he says.

The sustainability advantages of the Companion platform are also magnified as syringe size increases. By avoiding bulky exoskeletons or disposable add-on devices, Companion significantly reduces plastic waste and overall material usage – the benefits of which scale exponentially in larger barrel formats. Mr. Merhige says: “Pharmaceutical partners benefit not only from cost savings in packaging and logistics, but also from aligning with corporate and regulatory sustainability commitments.”

As biologics pipelines continue to expand, manufacturers require platforms that combine scalability, patient-centric usability, and operational efficiency. “The Credence Companion Syringe System sits at this convergence, enabling application of integrated safety and usability features across the full syringe range, supporting industry trends such as shortened 5mL barrels for 3mL dosing, and delivering measurable sustainability benefits,” he says.

## Datwyler Healthcare: Ensuring Integrity & Functionality

The biggest challenge in injectable delivery is ensuring the integrity and functionality of the primary packaging components to protect increasingly sensitive and complex drug formulations, especially biologics, explains Carina Van Eester, Global Platform Leader, Prefilled Syringes and Cartridges, Datwyler Healthcare.

**Datwyler Healthcare expanded its NeoFlex™ portfolio with new coated plungers, now available in sizes for large-volume containers.**



“This challenge goes beyond just producing a good component; it’s about a ‘zero defect’ philosophy that recognizes the critical role of primary packaging in the drug’s safety, stability, and efficacy,” she says.

Additionally, she says that regulations like USP<382>, which focuses more on the system instead of the component, and Annex 1, which requires a holistic approach to contamination control, require the support of knowledgeable suppliers who can work with the customers to bring new injectable drugs faster to the market.

“In close collaboration with partners, Datwyler has pioneered an industry-first: fully coated plungers in 5, 10, and 20mL formats—sizes that were not previously available on the market,” she says. “This expansion of our NeoFlex™ portfolio, which already included 0.5mL, 1mL long, 1–3mL PFS, and 3mL cartridge plungers, was developed with system thinking aligned to USP <382> requirements.”

She explains that large-volume plungers were once designed mainly for manual use or infusion pumps with small molecules that required no coating. With the shift toward subcutaneous administration of biologics, the demand for fully

coated plungers has grown. These plungers are critical to safeguard sensitive biologics from rubber extractables while ensuring consistent device functionality and accurate dosing.

“Our NeoFlex large-volume plungers are a critical component to guarantee good functionality of the new injection device,” says Ms. Van Eester. “NeoFlex plungers are also integral to the shift from traditional intravenous (IV) infusions to subcutaneous (SC) injections for patient self-injection. This advancement significantly improves patient comfort and convenience by eliminating the need for frequent visits to a hospital or clinic. Ultimately, this move toward at-home self-administration offers substantial benefits for the entire healthcare ecosystem. By reducing the reliance on costly clinical resources and professional healthcare staff, it leads to a total cost savings for both healthcare systems and insurers. The result is a more efficient, patient-centric, and cost-effective approach to long-term chronic disease management.”

## Lifecore: Incorporating New Drug Delivery Technologies Into Clinical & Commercial Manufacturing

New drug delivery technologies are transforming treatments within the injectables space by enabling new therapeutic options for previously unmet patient needs. For example, new technologies allow for higher concentrations of biologics to be delivered via injectables. While this is positive for patients, it poses manufacturing challenges. Higher concentrations can result in the formation of suspensions, which can increase formulation viscosity. Also, suspensions are difficult to maintain due to the potential for products to settle, creating complexity at multiple points in the manufacturing process and affecting the long-term stability of a product. With decades of expertise in sterile filtration and filling of highly viscous and complex products, Lifecore supports these types of delivery technologies and the formulations that incorporate them.

The novel use of polymers is also advancing the capabilities of injectables. Polymers are tunable and can thereby form delivery depots with improved targeting and sustained/controlled release of products. “Some of the formulations we manufacture use Lifecore’s hyaluronic acid (HA) to create a drug delivery depot that offers controlled release of a drug,” explains Ryan Swanson, PhD, Director of Process Development, Lifecore. “HA is often selected for these formulations because it is a naturally occurring biopolymer found throughout the human body, offering a safe vehicle for drug delivery. To date, Lifecore’s premium, pharmaceutical-grade HA has been incorporated in more than 150 million doses of injectable products worldwide. We continue to support the novel use of HA for clinical and commercial



**Lifecore is accustomed to overcoming complexities associated with novel drug delivery technologies.**

requirements by working with drug developers to create custom modifications for their unique formulations.”

### Nemera: Continuous Drug Delivery Accommodates Demanding Biologics

The biggest challenge in injectable delivery remains balancing patient comfort, safety, and adherence with the increasing complexity of current injectable therapies. Many new biologics, such as large-molecule drugs, require higher volumes, higher viscosity, and longer injection time.

“Conventional autoinjectors relying on spring forces to push drug quickly (in 10–15 seconds) could become impractical and painful for the patient as volume or viscosity increases,” says Corinne Malica, Marketing Global Category Manager, Nemera. “On-body delivery system devices address these challenges by allowing delivery of large volumes (up to 30 mL) over extended periods (several minutes up to an hour), at controlled flow rates that potentially mitigate patient pain and tissue stress, which eventually improves patient adherence.”

Nemera’s reusable on-body injector platform, Symbioze®, for continuous drug delivery is designed to accommodate the demanding requirements of biologic delivery – high-viscosity and large-volume formulations – with minimal patient discomfort, she describes. “Symbioze tackles this with a powerful miniaturized motor that can sustain controlled flow rates for very viscous solutions. It also allows programmable delivery profiles to accommodate drug characteristics and minimize injection force. Moreover, it integrates several key features – a reusable/disposable hybrid architecture for sustainability aspects, for large volume capacity and connectivity – setting it apart from other leading platforms.”

Symbioze provides audible and visual feedback to reassure the user that the dose is being delivered correctly. Large, tactile button and intuitive indicators make the injection experience as seamless as possible for patients of all ages, including those with limited dexterity. Finally, the combination of controlled flow, user-friendly, and intuitive interface is aimed at maximizing comfort and confidence during longer subcutaneous injections.

Ms. Malica says: “This platform was



Symbioze® on-body injector (Nemera).

designed with connectivity in mind, featuring built-in Bluetooth and integration with a dedicated app or cloud system to manage injection schedules, to send reminders and training prompts.”

In fact, she says that the future of injectable delivery is moving toward connected, intelligent devices that not only administer medication but also provide actionable insights for personalized care.

“As therapies become more complex, injectable delivery will evolve to be more comfortable, precise, and data-driven, ultimately improving patient outcomes and reducing the burden on healthcare systems,” she says. “By combining electro-mechanical reliability with digital connectivity, the device supports both patient adherence and clinician oversight. This addresses the dual challenge of improving patient experience while ensuring accurate, consistent drug delivery.”

### PCI Pharma Services: Early Integration of Drug Product With Device

One of the most persistent challenges in injectable drug delivery is balancing the increasing complexity of drug formulations

such as biologics, high-viscosity compounds, and novel modalities with the need for user-friendly, patient-centric delivery systems. As therapies shift toward self-administration and home use, delivery devices must accommodate larger volumes and more sensitive formulations without compromising ease of use, injection comfort, or dose accuracy. This is particularly critical for patients with limited dexterity or chronic conditions requiring regular injections.

“From a development and manufacturing perspective, integrating the drug product with the right device early in the

lifecycle is essential, yet it remains a challenge due to evolving regulatory requirements, variable regional preferences, and device availability,” says Dawn Manley, Director Global Technical Sales at PCI. “We see the greatest success when there is early collaboration between formulation, device, packaging, and regulatory teams to ensure the final product is safe, scalable, and aligned with patient needs across diverse therapeutic areas and global markets.”

As a CDMO, PCI Pharma Services partners with a range of biopharma companies and injection device manufacturers to support the development, sterile fill-finish manufacturing, assembly, testing, labeling and packaging of diverse drug-device combination products, including prefilled syringes (PFS), autoinjectors, pens, and on-body injectors. “PCI’s device-agnostic approach, combined with technical and regulatory guidance, enables clients to align their drug products with the most suitable delivery systems, ensuring a seamless path from development to commercialization in both North America and Europe,” she says.

The increasing complexity of injectable therapies demands flexible, scal-



able solutions that can accommodate varied formats across therapeutic areas and global markets. PCI's integrated services span clinical to commercial supply, managing intricate workflows and patient-centric design considerations while maintaining rigorous quality and compliance standards. Its capabilities support both high-volume treatments and personalized medicines.

PCI's recent acquisition of Ajinomoto Althea in San Diego significantly expands its sterile fill-finish capabilities in North America, particularly in syringe and cartridge filling, bolstering the CDMO's ability to support the increasing drug-device combination products across biologics, peptides, and small molecules. "Our adaptable tooling and assembly lines are designed to accommodate a wide range of device designs, materials, and configurations, enabling us to support clients in bringing life-changing injectable therapies to market with agility, precision, and patient-focused innovation," says Ms. Manley.

### Singota Solutions: Meeting the Multifaceted Challenges of Injectable Delivery

Despite advancements in biologics and drug delivery technologies, the biggest challenge in injectable delivery continues to be improving the patient experience sufficiently to maximize patient acceptance during the administration of complex molecules, according to Tim Wilson, Business Development Manager at Singota Solutions. This requires thoughtfully integrating formulation science, device engineering, usability, and regulatory compliance while ensuring product quality, safety, and accessibility.



As a one-stop-shop for early-stage, growing biopharma clients, Singota also offers cGMP cold chain services, including DSCSA-compliant 3PL, transportation testing, sample and dispense.

As an injectable medicine CDMO based in the US, Singota Solutions specializes in formulation development and aseptic filling. Singota serves as a one-stop-shop for early-stage, growing biopharma clients, offering cGMP cold chain services, including DSCSA-compliant 3PL, transportation testing, sample and dispense in Grade C suites, three sites in Europe, and labelling, packaging, and kitting services.

"The rapid growth of biologics, including monoclonal antibodies, gene therapies, and long-acting injectables, has redefined therapeutic possibilities, but introduced significant delivery hurdles," he says. "These molecules often demand high-concentration formulations with elevated viscosities and injection volumes, which can cause patient discomfort, require extended injection times, and test the limits of current device and container systems. Reformulation may help, but frequently impacts drug stability or shelf life, requiring extensive analytical and compatibility studies."

Drug-device combination products further compound the challenge, he adds. Devices must be mechanically sound and

intuitive for self-administration, especially for patients with chronic conditions, limited dexterity or needle anxiety. Designing delivery systems that meet user needs without compromising performance is a human factor and engineering challenge. This topic will take on increasing importance as healthcare continues to shift toward decentralized, home-based care, says Mr. Wilson.

Regulatory expectations around injectable drug products are increasingly rigorous. Developers must demonstrate safety and efficacy of the drug and its delivery system under real-world conditions. Human factors validation, extractables and leachables testing, and stability under intended-use scenarios all contribute to extended timelines and add development costs.

Cold chain logistics represent another challenge. Many injectable therapies require stringent temperature controls. Maintaining product integrity while enabling flexible and responsive supply chains, particularly for personalized therapies, demands robust quality systems and operational agility.

Accessibility must remain at the fore-

front. Injectable delivery technology innovation must be accompanied by strategies to scale manufacturing, streamline fill-finish operations, and reduce costs to support broader patient access, especially in resource-limited settings.

“Meeting the multifaceted challenges of technical and operational complexity as Singota accelerates client pathways to the clinic requires close collaboration across formulation, quality, and operational domains,” says Mr. Wilson.

### SCHOTT Pharma: Scaling Biologics Volumes to 5mL

One of the biggest challenges in injectable delivery lies in scaling biologics therapies to volumes of 5mL and more without compromising patient comfort, drug stability or operational efficiency. As biologics become more complex and potent, the need for high-volume subcutaneous delivery grows. Ready-to-use cartridges for large volumes are emerging as a transformative solution. These cartridges are designed to integrate seamlessly into wearable injectors or advanced autoinjectors, enabling subcutaneous delivery of viscous formulations over extended durations.

“Their robust design supports high fill volumes while maintaining container closure integrity, extractables/leachables compliance, and compatibility with high-throughput fill-finish operations,” says Dr. Robert Lindner, Global Product Manager Cartridges, SCHOTT Pharma. “Technically, these cartridges must balance several critical parameters: dimensional precision for device compatibility, barrier properties to protect sensitive biologics, as well as reliable break-loose and gliding forces to guarantee the consistent injection of biologics.”

Moreover, the shift toward nested, ready-to-fill formats is reducing line complexity and contamination risk during fill and finish, while supporting automation and scalability. As injectable therapies become increasingly personalized and data-driven, the supporting infrastructure, including the primary packaging, must evolve to enable seamless integration with intelligent delivery systems, he says. Smart cartridges with embedded data-matrix codes or RFID tags could enable real-time tracking of dose history and drug identity, enhancing pharmacovigilance, traceability, and personalization.

“SCHOTT Pharma is excited about the convergence of material science, device engineering, and digital health,” says Dr. Lindner. “Large-volume ready-to-use cartridges are no longer passive containers – they are enablers of next-generation therapies. As pharma moves toward decentralized care and patient self-administration, these cartridges will be central to delivering complex biologics safely, efficiently, and intelligently.”

### Stevanato Group: Addressing the Growing Complexity of Subcutaneous Delivery

The key to a successful launch and market penetration of biologics is the selection of the appropriate device like pens, autoinjectors or on-body delivery systems in combination with the most suitable container. The need to accommodate higher volumes, viscous fluids, an increasing number of longer-acting injectables with weekly, monthly or even longer dosing intervals, smaller batches, and the omnipresent need to reduce healthcare costs call for innovative and adaptable solutions. In addition, a user-friendly design with an ergonomic grip, an intuitive injection mechanism and safety features that prevent accidental needlestick injuries are just some of the additional challenges that need to be solved.

“An example that encompasses these features is the Aidaptus® autoinjector, developed by Owen Mumford and Stevanato Group,” says Adam Stops, Head of Product Management for Drug Delivery Systems, Stevanato Group.

Aidaptus is a two-step, single-use autoinjector compatible with prefilled



1mL or 2.25mL glass syringes. "These product features offer added value to pharmaceutical companies by delivering class-leading flexibility and adaptability in the development and manufacture of combination products," he says.

Aidaptus ensures drug visibility through the device's large window, allowing dose verification. It is designed to prevent needlestick injuries through a passively deployed needle shield, giving reassurance to patients with needle phobia by hiding the needle before, during, and after use. And, it features audible and visual notifications as clear feedback to the user for patient confidence and reassurance.

The ongoing trend of shifting from intravenous (IV) to subcutaneous (SC) drug delivery, which requires expanded treatment options with higher injection doses and more concentrated and highly viscous formulations, demands solutions that reduce the frequency of injections as offered by on-body delivery systems (OBDS). The Vertiva® OBDS, developed by Stevanato Group, uses a versatile platform technology, capable of delivering micro-precision basal doses or full-content bolus injections. The core

technology consists of a disposable injection unit called pod, a reusable smart controller that governs the activation process, and a proprietary, magnetically coupled drive mechanism connecting the pod to the smart controller enabling contactless power transmission between the two.

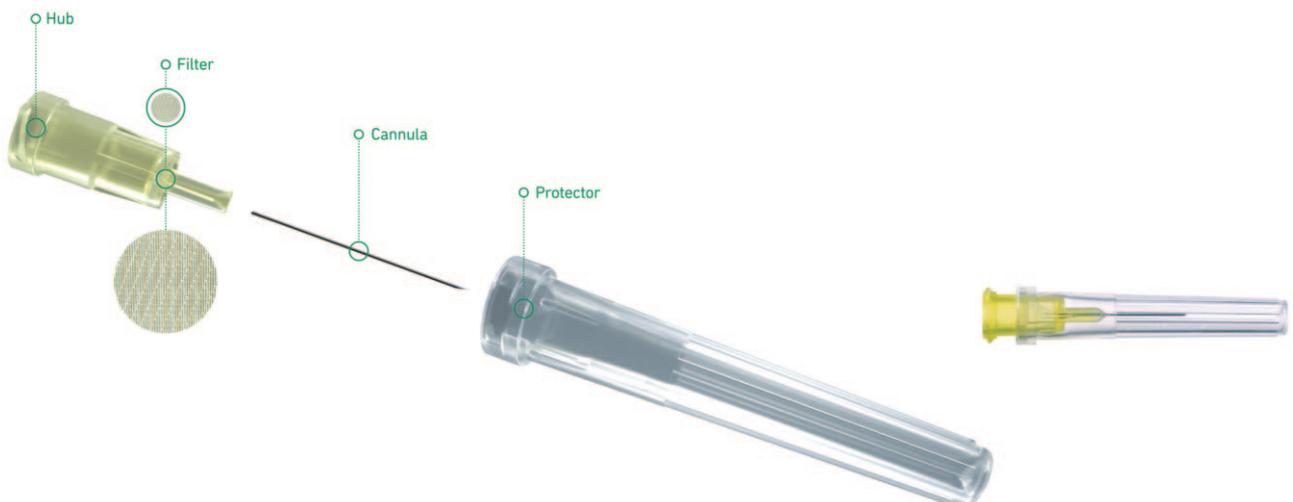
"One of the main advantages of OBDS is its ability to address the key challenge of medication adherence, part of the treatment effectiveness estimated to affect 30-40% of long-term patients," says Mr. Stops. "Vertiva stands out for its modular design and adaptability, supporting a wide range of therapies and delivery profiles within a single platform. Its flexible configuration – available in 3 and 10mL format – allows pharmaceutical companies to tailor the device to specific drug characteristics and patient needs, while maintaining ease of use and manufacturing efficiency. This makes it a practical solution for addressing the growing complexity of subcutaneous drug delivery."

## Terumo Pharmaceutical Solutions: Bridging the Gap in Ophthalmic Drug Delivery

The injection device represents a critical advancement in enabling the effective administration of injectable therapies for vision impairing diseases. Verified and validated for intravitreal applications, it serves as the essential link between pharmaceutical innovation and clinical implementation. Pharmaceutical researchers and drug developers have long recognized the significant burden of ophthalmologic conditions, responding with therapies that demonstrate proven clinical outcomes. Many of these treatments require precise delivery directly into the eye, a challenge that demands specialized technology. In alignment with its mission to support medical progress, Terumo has leveraged its deep expertise in injection systems to develop an intravitreal needle, facilitating reliable drug administration for ocular therapies.

"Current market offerings for medical devices validated for intravitreal injection often fall short of meeting the stringent requirements of pharmaceutical companies and regulatory authorities," says Thomas Issac, Product Manager for Injection De-

### Terumo's intravitreal injection solution.



vices at Terumo Pharmaceutical Solutions. “In response, Terumo has developed a solution that addresses these critical needs: a fully validated injection device supported by robust documentation. Leveraging its expertise in cannula design, needle manufacturing, and integrating advanced features – such as integrated filter – Terumo demonstrates a holistic approach to the unique challenges of parenteral ophthalmic therapy.”

He adds that the inclusion of a filter within the fluid path directly addresses concerns widely discussed in scientific literature regarding the presence of both extrinsic and intrinsic particulate matter in injectable formulations.

### West Pharmaceutical Services: Aligning All Facets of the Combination Product Lifecycle

One of the most persistent challenges in pharmaceutical packaging lies in aligning fragmented knowledge across stakeholders. While confidentiality is a necessary pillar of the life science industry, it can also hinder open dialogue. Companies are understandably cautious when it comes to sharing proprietary insights – yet without some degree of transparency, it's difficult to collaboratively address common obstacles. Creating environments where trust and discretion coexist is essential to moving forward.

This becomes particularly evident in the context of combination product development, where pharmaceutical companies often rely on several different suppliers for their device constituent part, says Dr. Bettine Boltres, Director, Scientific Affairs, Integrated Systems at West Pharmaceutical Services. “These collaborations frequently involve burdensome confidentiality agree-

ments (often even 3-way CDAs), inconsistent data sets, and a lack of synchronization across partners. As a result, it's not uncommon to see delays, miscommunication, and inefficiencies that could have been avoided with better-integrated workflows.”

With the rise in biologics, there is a concurrent rise in combination products – integrating drugs with device parts such as prefillable syringes. “Historically, pharmaceutical development and medical device engineering have followed distinct paths, each with its own regulatory logic, development priorities, and risk and quality frameworks. But as the two domains converge, a new paradigm will be emerging – one that demands alignment across all facets of the product lifecycle. Our industry is in the midst of a turning phase.”

Dr. Boltres says small companies, in particular, may struggle to navigate these complexities as they often lack experience with regulatory expectations or technical interdependencies, making it hard to anticipate issues before they arise. On the flip side, large global organizations can face challenges of their own – such as internal silos, overlapping responsibilities, or difficulty aligning across multiple business units.

This shift isn't limited to regulatory compliance. It begins much earlier, at the development stage, where a shared understanding of performance, safety, and quality objectives must guide design decisions. It also extends into risk management, where integrated assessment methodologies are increasingly needed to meet global expectations.

This evolution also affects the packaging sector. It's not just about protecting the product – it's about ensuring functionality, compatibility, and regulatory readiness

across an integrated platform. As such, the role of packaging suppliers is expanding into true system manufacturing, with responsibilities that mirror those traditionally held by device companies.

“The mindset of ‘component supplier’ no longer suffices. We are now responsible for delivering functional systems – fully verified and ready to support both pharmaceutical and device-level requirements,” she says.

In the end, the true hurdle is not a lack of expertise, but the scattered nature of that expertise. “Our goal should be to consolidate critical information, streamline communication, and support pharma partners in gaining a clear, system-wide understanding of their packaging choices,” she adds. “Only then can we reduce friction and deliver reliable, high-quality solutions that meet both technical and patient needs. In the coming years, this convergence will continue to reshape how therapies are designed, built, and regulated around the world. These currently parallel worlds – pharma and medtech – will eventually operate as one cohesive ecosystem.” ♦

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# Drug Development EXECUTIVE



Jacob Hunter  
Chief Business Officer  
ALZpath, Inc.



## ALZpath: A Diagnostic Assay Changing the Future of Alzheimer's Disease

ALZpath is a diagnostic solutions company committed to improving the lives of people suffering from Alzheimer's disease and related dementias. They are the developer and provider of a proprietary pTau217 antibody, which is rapidly becoming the new gold standard in blood-based diagnostic tests used to detect the presence and progression of Alzheimer's disease.

*Drug Development & Delivery* recently interviewed Jacob Hunter, Chief Business Officer, ALZpath, Inc., to discuss the development and deployment of the company's proprietary pTau217 antibody, bridging the gap between detection and treatment to improve patient outcomes globally.

### Q: What does ALZpath do?

**A:** Alzheimer's disease and related dementias affect 55 million people worldwide. Despite its prevalence, nearly 75% of patients, including millions with Alzheimer's disease, remain undiagnosed, depriving them access to clinical trials, new disease-modifying therapies (DMTs), specialized care, and, most importantly, valuable time as their condition worsens.

Recognizing the global need for accessible, affordable, and non-invasive Alzheimer's disease diagnosis tools, ALZpath democratizes access to vital diagnostic solutions by entering agreements and partnerships with leading diagnostic assay and analytic platform companies and research institutions. These agreements enable the ALZpath proprietary phosphorylated tau (pTau217) antibody to be incorporated into advanced blood tests and systems used for research and clinical purposes around the world. In doing so, ALZpath aims to support early detection, clinical trial enrollment,

and treatment monitoring to improve patient outcomes worldwide.

#### **Q: How was the idea conceived to create ALZpath?**

**A:** In early 2019, researchers began sharing groundbreaking findings that identified blood-based biomarkers – particularly, a protein called pTau217 – as a promising way to diagnose Alzheimer's disease. These findings were significant and timely, given the rising prevalence of Alzheimer's disease and related dementias, the inaccessibility and cost of the generally accepted diagnostic standards at the time (cerebral spinal fluid testing or PET imaging), and the advancement of disease-modifying treatments offering new hope for patients – but only when diagnosed.

ALZpath was founded based on the belief that widely accessible, precise blood-based diagnostic solutions would be required to address the lack of timely and accurate diagnoses of Alzheimer's disease and to make the potentially profound benefit of newer treatments and interventions more equitably and universally available to patients around the world.

#### **Q: Can you tell us your origin story?**

**A:** Eric Reiman, MD, a leading Alzheimer's disease researcher, collaborated with colleagues on a study affirming that pTau217 diagnostic assays outperformed MRI brain scans and were as effective as PET scans or cerebral spinal fluid testing - the current 'gold standard'- and could potentially provide patients with accessible, accurate testing in their local doctor's office.

In 2020, Dr. Reiman, Jerre Stead, and Venkat Shastri founded ALZpath, creating a nimble organization that could collaborate with researchers and scientists on new discoveries and quickly bring diagnostic solutions to market helping support the advancement of a new generation of treatments for Alzheimer's disease.

Building on prior research and guided by a distinguished group of scientific and clinical experts, ALZpath quickly and effectively designed, developed, and produced its proprietary pTau217 antibody which has proven to deliver significant and consistently reliable sensitivity when incorporated into assays for research and clinical applications across a variety of analytical platforms.

Today, ALZpath's scientific advisory board includes some of the world's leading researchers and clinical experts in Alzheimer's disease and other neurological conditions. The

company and its novel, award-winning pTau217 are paving the way for a bright future for the millions of current and future patients and caregivers, utilizing blood-based testing to usher in a new era of diagnosis and treatment for Alzheimer's disease.

#### **Q: How does the Immunoassay work and how was it developed?**

**A:** The pTau217 immunoassay is built on an ELISA-based sandwich format, known for its reliability and sensitivity in detecting Alzheimer's disease biomarkers. This antibody is uniquely effective across a variety of diagnostic platforms, whether it's used on a Quanterix SIMOA® platform, optimized for ultra-sensitive results or on Roche's high-throughput systems in commercial and clinical laboratories. This versatility makes the assay adaptable to both high-volume and more specialized clinical settings, positioning it as a powerful, non-invasive diagnostic tool for Alzheimer's disease.

Developing the assay presented unique challenges, especially in ensuring that the antibody could function effectively across multiple diagnostic platforms. ALZpath prioritized consistency and versatility, which has allowed the company to successfully deliver a solution that works across both low and high-volume commercial formats. This approach has been key to securing agreements to integrate the company's proprietary pTau217 antibody into several leading research use only (RUO), laboratory developed tests (LDT) and in vitro diagnostic (IVD) tests and platforms and ultimately helping ensure widespread access to next-generation treatments and other interventions to improve outcomes for patients.

#### **Q: How does ALZpath connect to drug development?**

**A:** ALZpath and its proprietary pTau217 antibody are uniquely connected across the entire continuum from drug discovery and development to treatment and monitoring. The antibody has been used in assays that were foundational to groundbreaking research into both the diagnosis and treatment of Alzheimer's disease. It is also incorporated into assays being used for research purposes as well as those currently under regulatory review for approval and use as invitro diagnostics (IVD) worldwide.

The ALZpath pTau217 antibody enters the market at a critical time for expanded and timely detection of Alzheimer's disease, addressing the pressing need for accessible diagnostic

tools. Early diagnosis is the key for patients to benefit from early access to clinical trials, advanced DMTs, specialized care, and improved outcomes.

Early, precise, and more widespread identification allows researchers to enroll more patients in trials for Alzheimer's disease treatments, and to more accurately understand and measure the impact of treatment and progression of their condition during trials to optimize outcomes.

**Q: Can you speak to the business model? What is your process when it comes to licensing agreements?**

**A:** ALZpath's business model is centered around providing access via licenses to our proprietary pTau217 antibody for RUO, LDT, and IVD use to partners who have the expertise to develop advanced assays incorporating our antibody, pursue and secure necessary regulatory approvals, produce at scale, and bring tests to market efficiently and effectively.

By leveraging the resources and reach of industry leaders, blood-based assays will become more rapidly and widely accessible, accelerating the availability of Alzheimer's disease testing across various regions, research environments and clinical settings.

ALZpath recently signed licensing agreements with global diagnostics companies Roche and Beckman Coulter who will develop blood tests using ALZpath's proprietary pTau217 antibody on their globally available platforms. The FDA has granted Breakthrough Device Designation (BDD) to both.

**Q: What is the projected impact?**

**A:** Our diagnostic technology has the potential to make a profound impact, particularly in accelerating the use and efficacy of DMTs for Alzheimer's disease. As we enter a critical period for these treatments, identifying and diagnosing patients earlier is essential to ensure they receive access to clinical trials and treatment and are treated when it is most beneficial. The accuracy and accessibility of assays incorporating ALZpath's pTau217 antibody means that more patients can be identified at a stage where these DMTs are most effective, improving patient outcomes. Ultimately, ALZpath aims to bridge the gap between diagnosis and treatment, ensuring that patients who need these therapies can access them as soon as possible, to improve care outcomes and quality of life for patients and caregivers.

**Q: Can you tell us the future of the antibody/blood-based tests? What is the roadmap?**

**A:** At ALZpath we recognize the profound burden Alzheimer's disease and related dementias place on individuals, families, caregivers, and communities. We also know that with timely and accurate diagnosis, targeted treatments, education, and comprehensive support, people will increasingly have opportunities to live well even after an Alzheimer's disease diagnosis.

Achieving this requires fundamentally rethinking the current approach to diagnosis, treatment, and care. With passion, creativity, and perseverance, we are steadfast in our mission to transform the Alzheimer's disease care paradigm and improve the lives of all those affected by this disease. With our pTau217 biomarker, there are three areas of development at the forefront:

**Improving Patient Identification & Selection for Clinical Trials:**

The incorporation of ALZpath's proprietary pTau217 antibody into highly sensitive blood-based research assays has and will continue to play a vital role in the development and successful advancement of new treatments for Alzheimer's disease. More widespread availability of highly sensitive blood-based tests utilizing our pTau217 biomarker will help to increase the percentage and number of patients that receive a timely and accurate diagnosis and can therefore be identified as potentially qualifying for a clinical trial. The success of clinical trials, particularly for a new generation of disease modifying therapies for Alzheimer's disease, is highly dependent on not only identifying a sufficient cohort of properly diagnosed patients, but also determining precisely where they are in the progression of their disease. Advanced research assays incorporating our pTau217 antibody can accurately detect the presence of Alzheimer's disease at the earliest stages, even before symptoms appear, helping to ensure that the condition of patients enrolled in trials has not advanced past the point where they are likely to benefit from the treatment. Lastly, the use of these advanced pTau217 blood tests also enables researchers to track the relative progression of Alzheimer's disease in patients over the course of the trial, thereby helping to generate evidence of whether a particular treatment is effective in slowing or perhaps even halting the progression of the disease, and over what period the impact endures.

**Expanding Access in Clinical Settings via Collaboration & Partnerships:** ALZpath is currently focused on expanding access through collaboration and partnerships with more IVD companies, broadening our geographical footprint, and incorporating pTau217 testing into additional clinical trials. Just as cancer treatments have evolved over the past 25 years from general chemotherapy to targeted therapies addressing specific mutations, we envision a similar shift in Alzheimer's disease care toward personalized medicine, which is even more of a reason to ensure pTau217 testing and other blood-based tests are broadly available in the clinical setting.

**At-Home Testing:** We are exploring potential opportunities to develop and offer at-home testing to expand accessibility of diagnostic tools for Alzheimer's disease and related dementias. At-home testing offers significant benefits for underserved populations who may face socioeconomic or geographical challenges, provides an additional tool for caregivers and the aging population, and could allow for ongoing treatment monitoring.

Empowered by ALZpath's success thus far, we remain deeply committed to our mission, and this is just the beginning. With scalable and convenient blood tests for Alzheimer's disease now within reach, the future of this disease – and its impact on patients – can change dramatically. Earlier diagnosis, coupled with DMTs and other emerging treatments, offers a brighter future for Alzheimer's disease patients and caregivers. ♦

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# FORMULATION DEVELOPMENT

## Innovative Drug Delivery Approaches for GLP-1 Agonists: Enhancing Medication Adherence & Treatment Outcomes

By: Nasrin Mahmoudi, PharmD, PhD, and Michael Baumann, PhD

### INTRODUCTION

Obesity is a major global health issue, affecting more than 890 million adults. In 2022, 2.5 billion adults aged 18 years and older were overweight.<sup>1</sup> Glucagon-Like Peptide-1 (GLP-1) receptor agonists have emerged as a revolutionary treatment for obesity, showing significant effectiveness in reducing weight by regulating appetite and energy balance.<sup>2</sup> However, most of the current GLP-1 formulations have limitations that can affect patient adherence and treatment success, such as frequent injections, gastrointestinal side effects, inconsistent and low bioavailability, as well as high price.

Advancements in pharmaceutical technology are paving the way for improving GLP-1 agonist formulations, delivery methods, and cost. These innovations aim to overcome existing challenges while enhancing therapeutic effectiveness. Optimizing delivery systems is crucial for long-term obesity treatment and medication adherence.

This article highlights recent developments in GLP-1 agonist formulations and delivery methods, including advanced injectable formulations (eg, prolonged release), novel oral delivery systems (eg, buccal tablets), and topical formulations (eg, transdermal patches). These advancements are vital for healthcare providers and researchers striving to improve obesity treatment outcomes.

### GLP-1 & GLP-1 ANALOGS

Glucagon-like peptide-1 (GLP-1) is a 37-amino acid hormone derived from the proglucagon gene, recognized for its wide-ranging pharmacological potential.<sup>3</sup> It is primarily secreted in the intestine in an inactive form, which is then enzymatically converted into its active variants. GLP-1 exerts its effects by binding to GLP-1 receptors (GLP-1R), which are predominantly found in the pancreas. This interaction promotes insulin secretion and inhibits glucagon release, contributing to reduction of glucose in blood.<sup>4</sup> Beyond the pancreas, GLP-1 receptors are also expressed in various organs, including the brain, heart, gastrointestinal tract, lungs, liver, kidneys, adipose tissue, and skeletal muscle, contributing to its diverse physiological roles.<sup>3</sup>

However, the active forms of GLP-1 have a very short plasma half-life (less than 2 minutes) due to rapid degradation by the enzyme dipeptidyl peptidase-4 (DPP-4).<sup>3,4</sup> This enzymatic cleavage not only inactivates GLP-1 but also generates metabolites that may act as antagonists at the GLP-1 receptor.<sup>3</sup> Because enzyme DPP-4 is mainly located on the surface of the intestinal cells, a large portion of GLP-1 is degraded to inactive metabolites, and only 25% of GLP-1 reaches the blood circulation.

GLP-1 analogs are peptides that were developed to mitigate the limitations associated with endogenous GLP-1, including the short plasma half-life ( $t_{1/2}$ ) and the rapid enzymatic degradation by DPP-4.

TABLE 1

Drug	Brand Name/ Manufacturer	Plasma t <sub>1/2</sub>	Administration / Indications	FDA Approval Date
Exenatide	Byetta®/ AstraZeneca	2-4 hours	Once or twice daily sc injections/type 2 diabetes	2005 - First GLP-1 analog approved by FDA
Liraglutide	Saxenda®/ Novo Nordisk	12 hours	Once daily/type 2 diabetes	2010
Exenatide ER	Bydureon®/ AstraZeneca		Once weekly sc injections/type 2 diabetes	2012
Albiglutide	Tanzeum®/GSK	120 hours	Once weekly sc injections/type 2 diabetes	2014
Dulaglutide	Trulicity®/Eli Lilly	90 hours	Once weekly sc injections/type 2 diabetes	2014
Lixisenatide	Adlyxin®/Sanofi	3-4 hours	Once daily/type 2 diabetes	2016
Semaglutide	Ozempic®/ Novo Nordisk	160 hours	Once weekly sc injections/type 2 diabetes	2017
Semaglutide	Rybelsus®/ Novo Nordisk		Once daily/Oral/ type 2 diabetes	2019 - First and only FDA- approved GLP-1 receptor agonist in tablet form

\*sc= subcutaneous

#### GLP-1 Agonists Approved by the FDA for the Treatment of Diabetes

## GLP-1 DRUGS & AVAILABLE DOSAGE FORMS

The first drug in this class for treatment of type 2 diabetes, Exenatide (Byetta®), received approval from the US FDA in 2005. More than a decade later, in 2017, long-acting and more potent GLP-1 analogs, such as Semaglutide, were developed (Table 1).

Semaglutide, initially approved in 2017 under the brand name Ozempic® for the treatment of type 2 diabetes, received FDA approval in 2021 as Wegovy® for obesity management. By that same year, it had become one of the top 100 most-prescribed drugs in the US.

## INJECTABLE DOSAGE FORMS

GLP-1 receptor agonists have emerged as effective pharmacological tools for managing obesity, with clinical trials demonstrating weight loss ranging from 5% to 15% of initial body weight over a 12-month period.<sup>1</sup> However, most of these agents require subcutaneous administration, which can negatively impact patient adherence due to the discomfort and inconvenience of regular injections.<sup>5</sup>

Currently, injectable GLP-1 analogs are divided into short- and long-acting drugs. Short-acting GLP-1 analogs (Table 2) reduce glucose response after eating food by increasing insulin secretion and delaying gastric emptying. Due to their short plasma half-life t<sub>1/2</sub> (~2-4 h), they are administered once or twice daily.

Short-acting GLP-1 analogs often result in fluctuating plasma concentrations, contributing to side effects and inconsistent therapeutic outcomes. These limitations have driven pharmaceutical research toward developing advanced delivery systems that maintain efficacy while improving patient compliance.<sup>1</sup>

One major advancement is the development of long-acting injectable formulations. These utilize technologies, such as microsphere encapsulation, depot systems, and molecular modifications, to extend drug release and reduce injection frequency.<sup>6</sup> Polymer-based microsphere systems, in particular, use biodegradable materials to enable gradual drug release, potentially supporting once-monthly or even less-frequent dosing schedules.

Forming depots *in situ* represents another innovative approach. In the body,

TABLE 2

Drug	Brand Name/Manufacturer	Description	Plasma t <sub>1/2</sub>	Administration/Indications	Key Features
Exenatide	Byetta®/AstraZeneca	Synthetic peptide derived from exendin-4, isolated from the Gila monster	~2-4 hours	Once or twice daily sc injections/type 2 diabetes	First GLP-1 analog approved by FDA; higher resistance to DPP-4 degradation
Lixisenatide	Lyxumia®/Sanofi	Derivative of exenatide with six lysine residues at the C-terminal	~2-4 hours	Once or twice daily sc injections/type 2 diabetes	4-fold higher affinity to GLP-1R; fewer episodes of symptomatic hypoglycemia

\*sc = subcutaneous

**GLP-1 Analogs: Short-Acting Drugs**

the liquid formulation converts to a gel system upon injection, allowing for sustained drug release through a matrix formation.<sup>1</sup> Molecular modification is used to reduce the susceptibility of the drug to enzyme degradation providing longer half-life.

**ORAL FORMULATIONS**

Oral tablets and capsules are considered the most convenient dosage forms for pharmaceuticals. Oral Semaglutide was approved by the FDA in 2019 as the first oral GLP-1 receptor agonist for type 2 diabetes. Oral Semaglutide has a lower bioavailability (0.8%) compared to subcutaneous Semaglutide but achieves therapeutic levels with once-daily administration. The half-life of oral Semaglutide is approximately 1 week, allowing for steady-state activity with daily dosing.

Formulating GLP-1 drugs for oral administration presents several challenges due to the inherent properties of peptides. Peptides are susceptible to degradation by stomach acid and digestive enzymes, which significantly reduces their bioavailability.<sup>7</sup> Additionally, the large molecular size and hydrophilicity of peptides hinder their absorption across the gastro-intesti-

nal epithelium.<sup>7</sup> By innovative approaches, such as using protective barriers, permeation enhancers, and advanced delivery systems to improve bioavailability, researchers are developing new GLP-1 analog drugs to make oral formulations a promising alternative for improving patient experience and adherence.<sup>5</sup>

**KEY APPROACHES TO OVERCOME CHALLENGES IN PEPTIDE DELIVERY**

- Protein engineering to resist enzymatic degradation
- Enzyme inhibitors and stabilizers for protection and stability
- PEGylation and albumin binding for half-life extension
- Enteric coatings for pH protection
- Encapsulation systems (eg, nanoparticles, liposomes)
- Permeation enhancers like SNAC
- Mucoadhesive systems for prolonged mucosal contact

Several of these approaches are achieved by use of appropriate excipients.

**ROLE OF EXCIPIENTS IN ORAL FORMULATIONS**

Excipients play crucial roles in enhancing the stability and bioavailability of oral GLP-1 formulations. Hydroxypropyl methylcellulose (HPMC), polyvinylpyrrolidone (PVP), and microcrystalline cellulose (MCC), to name a few, are commonly used as matrix formers, binders, and fillers in tablet formulations. MCC for example is one the excipients used in oral formulation of Semaglutide.<sup>8</sup> Another formulation aid that has been used in Semaglutide tablets is called SNAC (Sodium N-(8-[2-Hydroxy]benzoyl] Amino) Caprylate; Salcaprozate sodium), which is an absorption enhancer used to improve the bioavailability of peptide and protein therapeutics when administered orally. SNAC enhances absorption by neutralizing the pH in the stomach, protecting the drug from degradation by gastric enzymes and increasing membrane permeability.<sup>8</sup>

Often a combination of approaches is investigated to study GLP-1 absorption and stabilities. The use of hydrophobic polymers such as poly (lactic-co-glycolic acid) nanoparticles (PLGA NPs) in oral tablets and enzyme inhibitors may show potential for improving the oral bioavail-

TABLE 3

Drug	Brand Name/ Manufacturer	Description	Plasma t <sub>1/2</sub>	Administration/Indications
Exenatide ER	*Bydureon®/ AstraZeneca	~7-8 days	Once weekly	Gradual and sustained release; microspheres can cause irregular drug release
Liraglutide	Victoza®/ Novo Nordisk	~13 hours	Once daily	First long-acting GLP-1 analog; higher resistance to DPP-4 degradation
Albiglutide	Tanzeum®/ GSK	~5 days	Once weekly	Long-acting GLP-1 analog
Dulaglutide	Trulicity®/ Eli Lilly	~5 days	Once weekly	Long-acting GLP-1 analog
Taspoglutide	Pending FDA Approval	~7-8 days	Once weekly	Long-acting GLP-1 analog
Efpeglenatide	Pending FDA Approval	~7-8 days	Once weekly	Long-acting GLP-1 analog
Semaglutide	Ozempic®	~7 days	Once weekly	Long-acting GLP-1 analog
Tirzepatide	Mounjaro®/ Eli Lilly	~5 days	Once weekly	** Dual GLP-1/GIP receptor agonist; long-acting GLP-1 analog

#### GLP-1 Analogs: Long-Acting Drugs

ability of GLP-1 agonists.<sup>9</sup>

These technologies work together to protect the peptide from enzymatic breakdown while ensuring close contact with the intestinal tissue, thereby enhancing absorption. For example, encapsulation of Liraglutide, a long-acting GLP-1, in PLGA NPs significantly protected the drug from degradation in simulated gastric and intestinal fluids.<sup>10,11</sup> Another example is Octreotide (Mycapssa®), a synthetic analog of the natural peptide hormone somatostatin, which is formulated using enteric coating in combination with Transient Permeability Enhancer (TPE®) technology to facilitate oral delivery.<sup>17</sup> Enteric coatings are used in oral peptide formulations under development, but for oral Semaglutide an alternative strategy is used for gastric absorption rather than intestinal targeting.

Mucoadhesive hydrophilic polymers, such as POLYOX™ polyethylene oxide, are

other polymeric excipients that are investigated in buccal delivery systems, such as tablets and oral films.<sup>12-14</sup> In an older study, researchers investigated the absorption and effects of a mucoadhesive, biodegradable buccal GLP-1 tablets in 10 patients with type 2 diabetes.<sup>12</sup> Bilayer buccal tablets were prepared using POLYOX™ as an adhesive layer with a permeation enhancer. Therapeutic GLP-1 levels were achieved via buccal delivery and significant glucose-lowering effects in both fasting and postprandial states were observed.<sup>12</sup>

Another study explored the development of a bilayer buccal film designed to deliver a GLP-1 receptor agonist (GLP-1 RA) as a noninvasive alternative to injections for managing type 2 diabetes.<sup>13</sup> The film consists of a mucoadhesive layer containing the peptide and a backing layer to direct drug release unidirectionally. Using

biodegradable polymers and the permeation enhancer sodium glycodeoxycholate (GDC), the researchers aimed to improve peptide absorption through the buccal mucosa. Physicochemical characterization confirmed favorable properties, such as rapid disintegration, peptide stability, and good surface morphology. *Ex vivo* studies using porcine buccal tissue demonstrated that a 1:2 ratio of GLP-1 RA to GDC yielded the highest peptide flux, although higher GDC concentrations showed some tissue irritation. The findings support the potential of this bilayer film as a promising buccal delivery system for GLP-1 RAs, offering a patient-friendly alternative to injectable therapies. Such advancements in oral formulation technology represent a significant step toward making GLP-1 agonist therapy more accessible and acceptable to patients.

## EVALUATION OF ORAL GLP-1 RECEPTOR AGONISTS: SAFETY & EFFICACY CONSIDERATIONS

Although oral GLP-1 medications offer a more convenient alternative to injections, their safety is still under investigation. For instance, Pfizer stopped the development of danuglipron following a clinical trial incident involving liver-related complications.

To ensure the safe and effective use of oral GLP-1 therapies, continued research is essential. This includes evaluating their long-term safety, effectiveness, and drug-to-drug interactions.<sup>15</sup>

## ALTERNATIVE DELIVERY ROUTES & NOVEL APPROACHES

Recent advancements in drug delivery have opened new avenues for administering GLP-1 receptor agonists beyond traditional methods. Among these, transdermal systems, including patches, are being explored for their ability to provide sustained drug release while bypassing first-pass metabolism. These systems are not only noninvasive but also offer the convenience of easy removal. Intranasal delivery is another promising route, leveraging the nasal cavity's rich blood supply and permeability.

Although intranasal delivery of GLP-1 receptor agonists has not yet reached clinical application, extensive research on similar peptide drugs supports its potential. For instance, intranasal insulin has been widely studied for its ability to bypass the blood-brain barrier and achieve systemic effects, demonstrating the nasal route's viability for peptide absorption when combined with permeation enhancers and

mucoadhesive agents.<sup>16</sup> Similarly, calcitonin, a peptide hormone used in osteoporosis treatment, has been successfully delivered intranasally, offering a precedent for GLP-1 analogs.<sup>16</sup> These examples highlight the nasal mucosa's rich vascularization and permeability, making it a promising target for future GLP-1 delivery systems. With appropriate formulation strategies, including the use of absorption enhancers and protective carriers, intranasal GLP-1 therapies could offer a noninvasive, patient-friendly alternative to injections.

Microneedle technologies are gaining attention as a hybrid between injections and transdermal delivery. These tiny, minimally invasive needles can deliver GLP-1 agonists directly into the dermis, reducing discomfort and eliminating the need for sharps disposal. Innovations in dissolvable microneedles further support controlled release and patient-friendly administration.

## SUMMARY

Evaluation of drug delivery systems for GLP-1 receptor agonists from injectable to advanced oral, buccal, transdermal, and intranasal formulations has resulted in significant milestones in the treatment of obesity and type 2 diabetes. While injectable formulations remain effective, their limitations in patient adherence have driven innovation toward more convenient and patient-friendly delivery systems. Oral Semaglutide has paved the way for noninvasive alternatives, though challenges in peptide stability and absorption persist. Emerging technologies, such as mucoadhesive buccal films, microneedles, and transdermal patches, demonstrate prom-

ising potential to overcome these barriers, offering sustained release, improved bioavailability, and enhanced patient compliance. ♦

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# STERILE INJECTABLE MANUFACTURING

## Solving Complexity & Strategies for Commercial Success

By: Jennifer Gattari

### INTRODUCTION

The sterile injectable (SI) market is evolving rapidly, with significant growth being driven by trends ranging from the continued rise of biologics, biosimilars, and peptide therapeutics to the increased demand for patient-centric delivery formats.

As more complex SI therapies progress through late-stage clinical phases, the transition to commercial readiness is bringing new technical and operational challenges. As well as regulatory expectations becoming more rigorous, manufacturing facility infrastructure must now support a wider range of formats and sensitive formulations without compromising quality. Manufacturers also need to maintain sterility while delivering at greater volumes and speeds. Successfully navigating this shift calls for a strategic, forward-looking approach.

The following explores the key forces driving change in the SI space and outlines the core considerations manufacturers must address to deliver safe, effective therapies at commercial scale and the growing reliance on contract manufacturers to help navigate complexity with confidence.

### THERAPEUTIC INNOVATION IS RESHAPING MANUFACTURING EXPECTATIONS

The SI market is entering an exciting era of growth and opportunity. Valued at approximately \$732 billion in 2023, the SI market is projected to nearly double, reaching \$1.4 trillion by 2030.<sup>1</sup> However, as the landscape evolves, manufacturers are facing new complexities. The therapies moving through pipelines

today are not only more advanced but also more sensitive and specialized. This rising complexity is being driven by several key trends:

- **The Expanding Biologics Market:** Biologics have revolutionized treatment for complex, immune-mediated, and rare chronic conditions (eg, severe asthma, inflammatory bowel disease), offering targeted therapies where small molecules often fall short. Despite significant market growth, these products introduce challenging manufacturing requirements. These include the need for specialized processes, controlled environments, and advanced handling procedures across the supply chain.
- **A Growing Demand for Biosimilars:** The biosimilar market is also expanding, providing more cost-effective access to essential therapies. Although they offer a different route to market, biosimilars must still meet the same standards for product consistency, comparability, and regulatory compliance as their reference products.
- **Novel SI Therapeutics Entering the Pipeline:** Exciting new therapeutics, including peptides like GLP-1 analogues, are entering the market. With strong demand and accelerated development timelines, these therapies are advancing quickly. As they move toward commercial scale, they bring specific challenges related to product sensitivity, cold chain logistics and process control.

In addition to these trends, SI developers and manufacturers must also navigate the rising need for patient-friendly delivery formats, particularly as the demand for self-administration options rises. As a result, pre-filled syringes, cartridges, and autoinjectors are becoming more common across a range of therapeutic areas.

While these formats improve the patient experience, they also introduce added complexity for manufacturers. Fill-finish operations, for example, must be flexible enough to support multiple configurations while maintaining sterility and consistency. Additionally, these new container-closure systems will need to be validated for compatibility. Production processes must also be robust enough to support commercial-scale volumes without compromising product quality.

## A GROWING RELIANCE ON EXTERNAL MANUFACTURING EXPERTISE

As the complexity of SI manufacturing continues to rise, the combination of advanced product requirements, accelerated timelines, and evolving delivery formats is placing unprecedented pressure on internal capacity and capability.

As a result, many pharmaceutical companies are turning to contract manufacturing organizations (CMOs) for support. This growing demand is reflected in the SI contract manufacturing market, which was valued at approximately \$15.96 billion in 2024, and is projected to reach between \$31.9 billion and \$50.38 billion by 2030 to 2034.<sup>2</sup>

To effectively meet the needs of increasingly complex SIs, these CMOs need



to offer more than operational capability. They must provide a strategic approach to commercial manufacturing, one that anticipates complexity and embeds flexibility while supporting consistent delivery throughout commercial supply.

## HOW CMOS ARE HELPING TO PREPARE FOR SI MANUFACTURING COMPLEXITY

Achieving commercial readiness for increasingly complex SIs relies on the ability of manufacturers to overcome a range of technical, regulatory, and operational hurdles. CMOs can help SI developers respond effectively to these challenges by applying strategic, experience-led approaches that anticipate complexity rather than react to it, taking into account the following four key areas:

**1. Managing Regulatory Complexity:** The regulatory environment for SIs has always been stringent, built to protect patients by mandating consistent high-quality and safety. However, in recent years, expectations have become even more stringent. The introduction of the revised EU GMP Annex 1 has raised the bar for con-

tamination control, environmental monitoring, and aseptic processing. These updates reflect a wider regulatory shift toward greater scrutiny of sterility assurance, especially in light of more complex products, formats, and production environments. In parallel, the growth of combination products, including autoinjectors and pre-filled syringes, has introduced a different challenge. These products are subject to dual regulatory oversight, requiring compliance with both pharmaceutical regulations and medical device standards, including 21 CFR Part 820 and ISO 13485. From design control and human factors validation to labelling, traceability, and post-market surveillance, these overlapping requirements affect every stage of commercialization. Many CMOs are taking a proactive approach to managing these increasing regulatory demands:

**Positioning regulatory expertise at the core of project planning:** By integrating regulatory specialists early into cross-functional teams, CMOs can influence critical decisions around facility design, environmental control, and aseptic processing from the outset. This early involvement helps align operations with current regu-

latory standards while building the flexibility needed to adapt to future expectations.

**Developing a unified compliance approach for combination products:** Addressing dual regulatory pathways from the outset is essential for SI commercial success. CMOs can reduce complexity and avoid delays on the pathway to market by developing clear, integrated roadmaps that align pharmaceutical and device requirements within a single, coordinated framework.

**Designing documentation for inspection from day one:** By developing validation master plans, audit trails, and process justifications that reflect a risk-based approach, CMOs can reinforce control across critical operations and build confi-

dence in the robustness of their manufacturing processes. This level of documentation supports inspection readiness while also demonstrating a proactive commitment to quality.

**2. Tech Transfer With a Risk-Based Mindset:** For CMOs supporting SI products, tech transfer is a strategic, high-stakes process that can make or break a commercial launch. Success relies on approaching tech transfer with structure, discipline, and a clear understanding of product- and process-specific risks from the outset. Experienced CMOs will apply a backward design approach to tech transfer, starting with the final critical quality attributes (CQAs) that define patient safety and product performance. Every aspect of the transfer, from material flow to environ-

mental control, must be assessed against these CQAs to ensure that what works at development scale can be executed reliably at commercial volumes. These CMOs will also carry out early, detailed gap analyses to identify potential disconnects between the sending and receiving sites, including differences in equipment, process parameters, facility design, and documentation. Addressing these proactively helps prevent avoidable deviations and delays once production begins. SI tech transfer strategies must also reflect an in-depth understanding of product sensitivity. CMOs should incorporate controls to mitigate known risks such as temperature excursions, oxygen exposure, and shear stress during filling. These variables, if not carefully managed, can compromise product integrity and quickly erode confidence in the commercial process.

**3. Ensuring Sterility at Scale:** Maintaining sterility is essential in sterile injectable manufacturing, but it becomes more challenging as products move from late-stage clinical to commercial production. As batch sizes grow and fill speeds increase, there is greater potential for variability. To help ensure sterility and product quality at scale, manufacturers must implement tightly controlled, well-optimized processes designed to deliver precision and consistency every time. For biologics and peptide-based therapies like GLP-1 analogs, the demands are even higher. These products are often sensitive to temperature fluctuations, shear forces, and oxygen exposure, all of which are amplified under commercial manufacturing conditions. Even minor deviations during fill-finish operations, such as during capping or inspection, can impact product integrity and lead to costly delays or rework. To address



these risks, CMOs with extensive experience supporting complex SIs will apply a deliberate, science-led strategy:

**Validate fill-finish performance under commercial conditions:** By replicating commercial batch sizes, line speeds, and container types during process development, CMOs can uncover and address sources of variability before routine production begins, reducing the risk of sterility failures later on.

**Design processes around product-specific sensitivities:** Whether it's temperature shifts, oxygen exposure, or shear stress, experienced CMOs can tailor handling and process controls to match the unique characteristics of each molecule. These sensitivities inform every aspect of fill-finish set-up, including container selection and line configuration.

**Control critical variables with real-time oversight:** Maintaining sterility at scale depends on precise control of fill volumes, container closure integrity, and line speed. By applying in-line monitoring and rigorous process control, CMOs can help ensure every batch meets exacting quality standards, right from the start.

**4. Infrastructure & Equipment Readiness:** As SI therapies become more intricate, the infrastructure and equipment required to support commercial production must keep pace. Many of today's complex SI products, including lyophilized formulations, sensitive biologics, and device-integrated presentations, demand more than a traditional cleanroom set-up. Isolator-based fill-finish systems, format-flexible equipment, and advanced automation are becoming essential features of modern manufacturing environments. For CMOs,

deliberate investment in fit-for-purpose infrastructure is needed to accommodate this complexity. Facilities must be designed to support a range of formats without triggering full-scale revalidation with each new configuration. This kind of flexibility is critical for efficiency as well as for maintaining sterility and quality across varied presentations. Retrofitting older facilities to meet these needs can introduce significant challenges, including equipment compatibility issues, extended timelines, and limits on future scalability. Experienced CMOs will take a forward-looking approach, one that ensures equipment specifications align closely with product handling requirements from the outset. The goal is not just to deliver operational readiness, but to create a manufacturing environment built to adapt as product portfolios evolve.

## SETTING THE FOUNDATION FOR FUTURE COMMERCIAL SUCCESS

The SI market faces a future defined by increasing complexity, significantly escalating the demands placed upon commercial manufacturing capabilities. Meeting these sophisticated challenges effectively calls for a growing reliance on contract manufacturing organizations (CMOs) that apply proactive, strategic approaches to manufacturing. By engaging with CMOs capable of managing this complexity with proven, practical strategies, SI developers can help ensure vital therapies reach the patients who need them. ♦

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# LIPID SOURCING & SELECTION

## Navigating the Lipid Landscape: Overcoming the Challenges of Lipid Sourcing & Selection for LNPs

By: Donald Kelemen, PhD

### INTRODUCTION

Lipid nanoparticles (LNPs) represent one of the most significant advances in drug delivery technology in recent decades. Gaining prominence during the COVID-19 pandemic as the delivery vehicle for mRNA-based vaccines, LNPs have since attracted significant interest and investment, and their potential has never been more apparent.

LNPs offer numerous advantages that make them increasingly valuable in modern medicine — from safe and effective delivery of nucleic acid cargo to cell-free manufacturing processes and ease of production scale-up. But the path to developing successful LNP-based therapies and bringing them to market is far from straightforward.

Perhaps one of the most significant challenges lies in selecting and sourcing the molecules at the heart of LNPs: lipids. Lipids can impact anything from particle size and encapsulation efficiency to circulation time and cellular uptake. The right choices can optimize stability, efficacy, and scalability, while the wrong ones can introduce roadblocks that are difficult (and costly) to overcome. Even small variations in lipid composition can lead to significant functional changes in LNPs; selecting and sourcing the right lipids can therefore be highly complex and present numerous challenges.

So what are the biggest pitfalls in lipid selection and sourcing, and how can developers begin to navigate them?

### THE HIDDEN CHALLENGES OF LIPID SELECTION

The therapeutic success of an LNP formulation depends on choosing the right combination of lipids. Each lipid serves a distinct and critical role in the LNP complex, and the performance of an LNP formulation is directly tied to the composition and characteristics of the lipids it contains. The importance of the lipid selection process, then, cannot be overstated.

However, navigating the vast landscape of lipid options remains a complex and difficult task. There are a handful of lipids used in LNP-formulations, including cationic lipids, ionizable lipids, phospholipids, sterol lipids, and PEGylated lipids. Each lipid type is associated with a unique set of challenges and limitations, which must be carefully balanced with its advantages.

Some lipids, particularly cationic lipids, have largely fallen out of favor due to issues with toxicity and immune activation presenting serious safety concerns. However, even lipids that are well-established in LNP systems can present developmental challenges that can impact formulation performance and long-term viability.

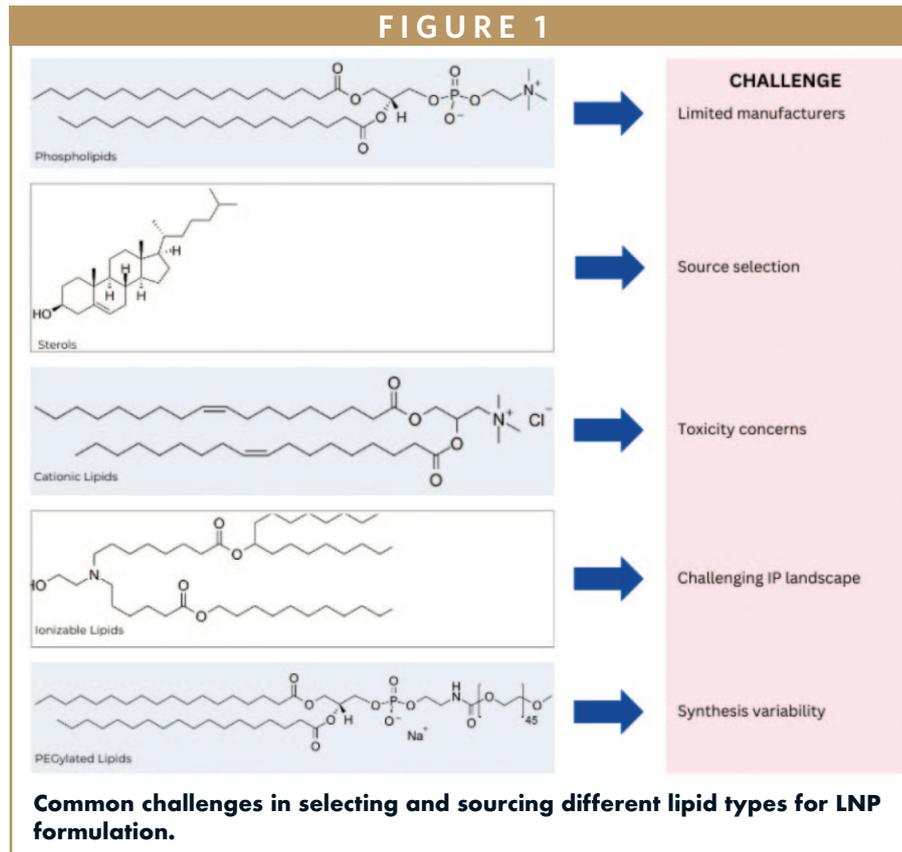
Take PEGylated lipids, for instance. These lipids are widely used in formulations and, despite comprising the smallest percentage of lipid components in LNPs, they play a vital role in increasing circulation time, improving steric stability, and modulating size. However, due to their amorphous structure, synthesizing PEGylated lipids is inherently difficult. When synthesis isn't carefully controlled, it can lead to a broad distribution of PEG molecule chain lengths — a factor that can impact LNP structure and function. This variability becomes a major concern when scaling up the manufacturing process, as it can be challenging

to maintain batch-to-batch consistency and requires considerable expertise and experience in lipid synthesis and characterization.

Beyond structural and manufacturing difficulties, lipid selection is also impacted by legal and commercial challenges. Ionizable lipids, for example, are widely used for their ability to change their charge based on the pH of their environment — being neutral at physiological pH but positively charged in more acidic conditions — making them extremely valuable in the LNP complex. Serving a multifunctional role in supporting nucleic acid complexation and endosomal release, they are considered a safer alternative to cationic lipids.

But, while these characteristics are desirable, using ionizable lipids in LNP formulations means developers must navigate an intellectual property (IP) “minefield.” The ionizable lipid IP landscape is crisscrossed with broad and vague patents that make it difficult to create a novel version without other companies claiming infringement. It is easy for large, well-funded organizations to tie up smaller ones in legal costs — even if the supposedly infringing company’s ionizable lipid is truly novel.

Because the vast majority of ionizable lipids currently used in commercial therapeutics are already patented, unless developers want to pay a licensing fee, they will need to customize these lipids. This brings fresh challenges around adherence to strict regulatory requirements and demands significant time and resources. Developers looking to create their own customized ionizable lipids should therefore consult both chemistry and legal experts who are deeply familiar with the space and start planning early to minimize



program delays and disruption.

Beyond ionizable and PEGylated lipids, additional components like phospholipids and sterol lipids can also present unique challenges. Phospholipids, often referred to as “helper lipids,” play a fundamental role in promoting structural integrity and modulating membrane fluidity and endosomal escape. However, despite their importance, there is a shortage of commercially orientated expertise in this space, making it difficult to find a manufacturer that can synthesize phospholipids for LNP therapeutic applications. In the case of sterol lipids (such as cholesterol), the challenge lies in selecting the source of the molecule, with synthetic cholesterol offering fewer safety concerns and regulatory issues than mammalian and plant-derived cholesterol.

Ultimately, choosing the right lipids isn’t only about their functional performance within the LNP — it’s also about understanding the regulatory, legal, and

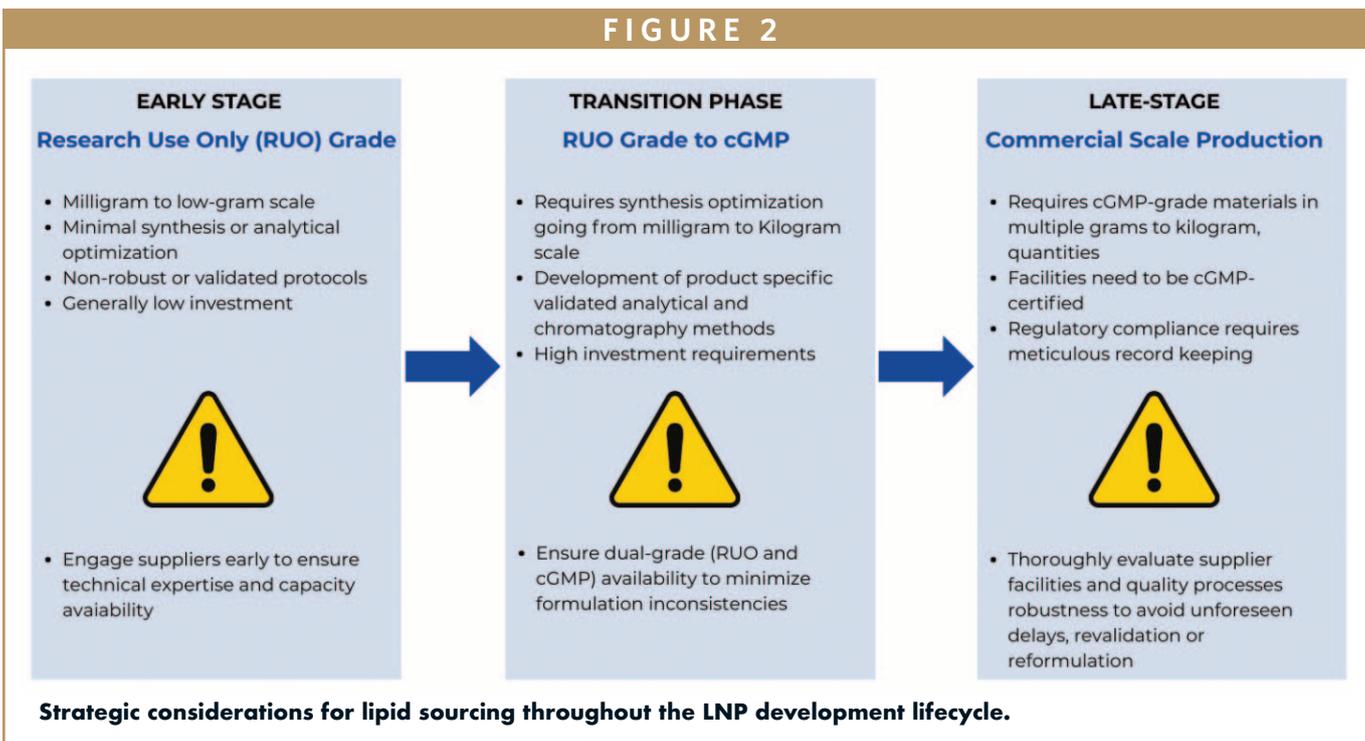
manufacturing implications that come with them. Making the right choice requires a deep understanding of the lipid landscape, from the intricacies of lipid chemistry to the complexities of LNP IP.

## PURITY MATTERS: A CRITICAL HURDLE IN LIPID DEVELOPMENT

Even when the right lipid has been identified, success depends on the ability to produce it consistently at a high standard of purity. Lipid purity is a non-negotiable factor in LNP formulation, as even small levels of impurities can introduce safety risks (through toxicity or immunogenicity) and impact LNP formation, stability, and biological activity. While it is possible to consistently create lipids with >99% purity with the right expertise and quality assurance systems, it is far from easy.

As every lipid is structurally different,

FIGURE 2



the purification process must be specifically refined and tailored to each one — a costly and time-consuming process that requires highly specialized expertise. And as production scales up, so do the challenges. Purification methods that work at milligram or gram scale don't often translate cleanly to kilogram-scale production, requiring further refinement. Moreover, not every facility is equipped with the specialized equipment needed to support large-scale lipid purification, such as large chromatography columns, which are not universally available.

Part of the challenge of purification lies not in the process itself but in the analysis. Due to their structural diversity and lack of chromophore, standard methods of purity analysis aren't sufficient, and manufacturers must rely on more advanced analytical techniques. As with the purification process, the analysis must be tailored to each individual lipid, making this a time-consuming task in its own right.

Ultimately, achieving cGMP-grade lipids at scale is not a trivial undertaking. It requires a purpose-built quality system,

a deep bench of expertise, and a clear understanding of how purification and analytical methods must be adapted to manufacturing at scale.

### THE STRATEGIC CHALLENGE OF SOURCING LIPIDS FOR LNPS

Moving from early stage LNP formulation to commercial production requires companies to strategically plan their lipid sourcing. Even when the ideal lipid structure has been identified and a reproducible purification process is in place, success ultimately depends on the ability to source that lipid consistently, at scale, and in compliance with regulatory standards. For developers, this can represent persistent challenges that must be addressed strategically to avoid delays, added costs, or formulation setbacks.

#### Initial Lipid Optimization

In early LNP development, only small quantities of lipids are required for screening and optimization, meaning that devel-

opers can use research use only (RUO) grade materials sourced from a suitable partner. At this stage, it can be difficult to manage costs as small quantities typically carry price premiums; additionally, finding lipid suppliers with the technical expertise and capacity needed to troubleshoot and optimize formulations can be challenging. This is especially true when working with customized lipid structures, where more specialized knowledge may be required.

#### Maintaining Continuity: From RUO to cGMP

One of the earliest stumbling blocks in lipid sourcing is the transition from RUO materials to the larger quantities required for clinical trials. Many suppliers only offer RUO-grade products, leaving developers with no choice but to switch vendors mid-program — a move that introduces uncertainty, potential performance changes, and costly revalidation.

To avoid this disruption, teams can look to engage suppliers that offer both RUO and cGMP versions of the same lipid early in the development process. This

continuity not only helps streamline the transition into clinical phases but also reduces risks of LNP formulation inconsistencies.

### Planning for Scale

Moving from the small quantities required in early stage studies to the larger quantities needed for clinical and commercial production presents another difficulty. Clinical programs typically need cGMP-grade materials in multiple grams to kilogram quantities — something that not all suppliers are equipped to handle. Producing high-quality, cGMP-compliant lipids at scale requires manufacturers to operate cGMP-certified facilities, which must meet extensive regulatory requirements and maintain thorough documentation.

To consistently produce cGMP-grade materials at scale, suppliers must have robust quality assurance systems. It is therefore essential to thoroughly evaluate supplier facilities and quality processes when moving into large-scale production. Identifying partners with proven capabilities early on can help developers avoid costly delays, revalidation work, or reformulation further down the line.

### Anticipating Potential Delays

Lead times for high-purity, cGMP-grade lipids can stretch for months, making the transition from early research to large-scale production both time-sensitive and operationally challenging. Any delays can put pressure on timelines and increase the risk of program disruption. To mitigate this, developers should engage with lipid suppliers as early as possible and proactively plan for their scale requirements. Working with lipid providers who have expertise in lipid synthesis and analytical development — and who support programs across all stages — can significantly reduce timelines and minimize disruption when moving between phases.

## BUILDING THE FOUNDATION FOR LNP SUCCESS

Lipid selection and sourcing are not only matters of function and convenience, they are strategic decisions that must consider scalability, regulatory demands, and commercial viability from the start. Each choice, whether related to lipid structure, purity, or supplier, can have far-reaching implications across the entire LNP lifecycle.

Success depends on selecting lipids that not only perform effectively within the formulation, but are also free from legal red

tape, can be purified to a high standard, and sourced reliably at scale. For developers looking to create a novel LNP therapeutic, failing to anticipate or fully recognize the challenges of lipid selection and sourcing can create delays, increase costs, and potentially derail otherwise promising programs.

Effectively navigating the complexity of the lipid landscape requires not only deep industry expertise, but the strategic foresight to align scientific, legal, and manufacturing requirements from the very beginning. ♦

### BIOGRAPHY



**Dr. Donald Kelemen** is Chief Scientific Officer at ABITEC Corporation, a global leader in lipid chemistry and formulation technologies for pharmaceutical and nutritional applications. He oversees the development of high-purity lipids and custom excipients that support a wide range of advanced therapeutic platforms, including lipid nanoparticles (LNPs). He earned his PhD in Nutrition and Biotechnology and has more than 20 years of experience in the pharmaceutical industry.

# TARGET DISCOVERY PLATFORM

## Multi-Omics, SITESEEKER® Technology & the Future of Targeted Protein Degradation

By: Alberto Moreno, PhD, and Laura Butler, PhD

### INTRODUCTION

The evolution of multi-omics-based approaches and large-scale sequencing for target discovery has contributed significantly to the identification of genes involved in currently incurable dis-

eases, paving the way for the development of new therapies. The development of gene editing technologies, such as gene-trap, RNAi, and CRISPR, have allowed for genome-wide perturbation studies using high-throughput screening assays (arrayed and pooled) that permit the identification of previously unknown target

FIGURE 1

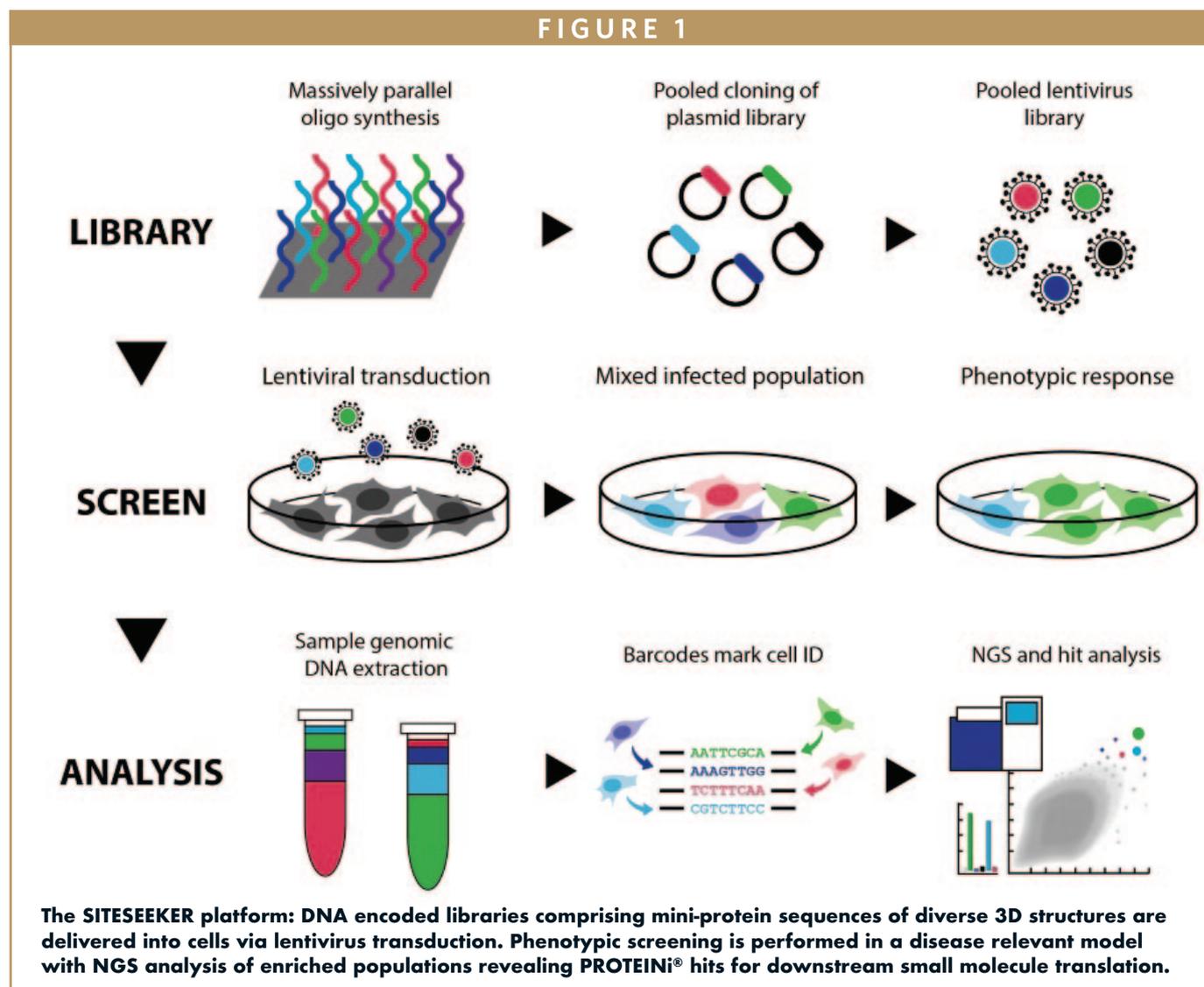
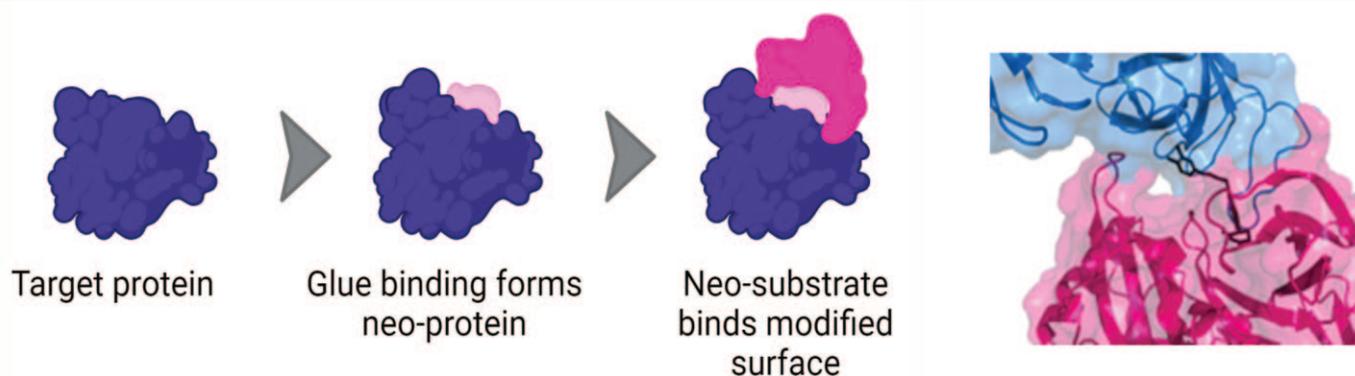


FIGURE 2



**Molecular glue degraders: Molecular glues enhance affinity or bind to a new target protein, modifying the surface properties to form a neo-protein that can now be recognized by a neo-substrate. In the case of molecular glue degraders, the target protein or neo substrate is a component of the UPS, targeted the novel binding partner for degradation (Image Created with BioRender.com)**

candidates.<sup>1</sup> However, there are challenges associated with these technologies as they do not directly provide functional characterization or inform on the presence of well-defined drug pockets or enzymatic activity of the target genes.

## FUNCTIONAL GENOMICS & SITESEEKER®

The strong dependence on protein-protein interaction interfaces for signaling cascades and the necessity of identifying small molecule pockets remain significant challenges in early drug discovery. The advent of new technologies that can identify previously unknown druggable pockets on target proteins present innovative approaches for the discovery and development of small-molecule therapeutics. In recent years, we have introduced SITESEEKER. This cutting-edge target discovery platform utilizes programmatically controlled hyper-diverse libraries of highly active mini-proteins called PROTEINI®. These fragments are designed to maximize stability and present novel three-dimensional conformations and are delivered into cells via lentiviral vectors.

Following the screening process, cells are harvested and genomic DNA from populations of interest (selected based on phenotypic responses or markers of interest) isolated and enriched, or depleted. PROTEINI identified through next-generation sequencing and bioinformatic data analysis (Figure 1). The application of SITESEEKER in high-throughput functional screening campaigns in disease-relevant cell models presents a promising avenue for the discovery of novel therapeutic targets that might be missed by conventional approaches. However, the potential of SITESEEKER extends beyond mere target identification. By integrating advanced computational tools for library design and experimental techniques for screening and reporter cell line generation for phenotypic assays, this technology also has the potential to map intricate protein interaction networks, revealing previously uncharacterized biological pathways and molecular mechanisms. These insights are crucial for understanding disease pathology at a deeper level and for developing targeted interventions that are both precise and effective.

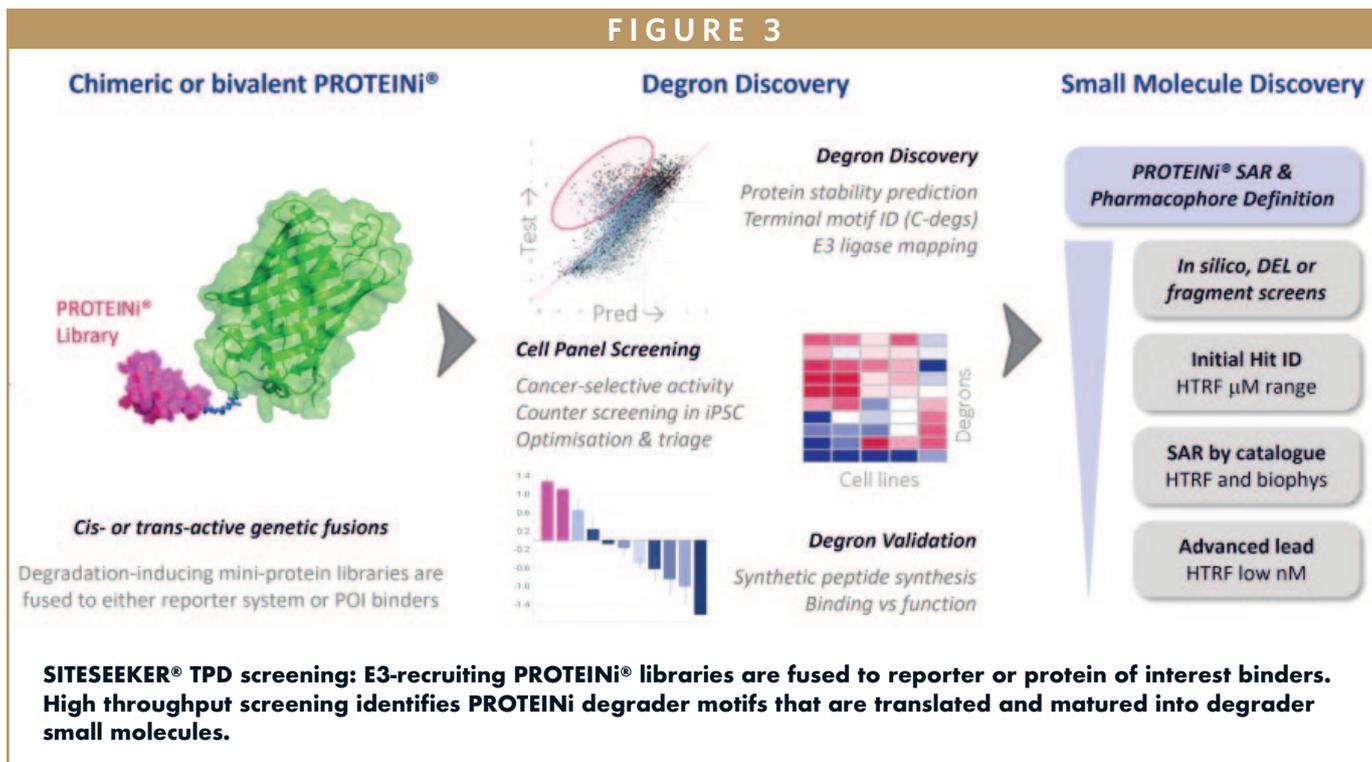
The application of SITESEEKER technology to a broad range of therapeutic

areas, such as oncology, neurodegeneration, and immunology, underscores its versatility and potential for delivering first-in-class drugs to a wide spectrum of patients in need. Its versatility has allowed expansion of the technology into the field of targeted protein degradation (TPD), an emerging area of biomedical research focused on developing therapeutic strategies that selectively degrade proteins of interest within cells using their own destruction machinery. The highly tunable library-based approach of this technology provides a unique ability to target the druggable space with alternative mechanisms of action to existing approved drugs, opening up new opportunities for the development of bivalent and monovalent degraders.

## TARGETED PROTEIN DEGRADATION - HETEROBIFUNCTIONAL & MOLECULAR GLUE DEGRADERS

The concept of modulating the turnover of specific proteins of interest using the ubiquitin-proteasome system (UPS) has garnered significant attention as

FIGURE 3



a mode of therapeutic intervention since the initiation of the first PROTAC clinical trials in 2019.<sup>2</sup> The engineered recruitment of this cellular machinery to eliminate disease-related proteins has become a significant focus of drug development activities and clinical trials in recent years.

TPD discovery efforts can be divided into two categories: bivalent and monovalent degraders. Bivalent degraders are composed of two key moieties, one that recruits a ubiquitin ligase (E3 ligase) and one that binds to the target protein of interest, with a linker connecting the two parts. In contrast, monovalent degraders or molecular glues are not composed of two distinct ligands but rather are small molecules that bind to one protein, modifying the surface properties in such a way that enhances binding of an existing interactor or, more excitingly, creating a binding face for novel interactions.<sup>3</sup> Through this modality, molecular glue degraders can bring E3 ligases into close proximity to neo-substrates, catalyzing their ubiquitination and subsequent degradation (Figure 2).

The generation and development of TPD drugs is now a well-defined process, generating a constant flow of molecules that have gradually increased in presence in clinical testing. Although more efficacy and safety evidence is needed, protein degraders are showing promising activity as cancer therapies.<sup>4</sup> There are more than 600 different E3 ligases in the human proteome; however, only a limited number are currently being used for degrader-based therapies – mainly Cereblon (CRBN) and Von Hippel-Lindau (VHL). In both cases, there have been challenging limitations associated with tolerance, resistance, pharmacokinetic properties, and oral bioavailability.<sup>5</sup> One of the problems associated with bifunctional degraders is that the rule of five (chemical properties that define druggability) for small molecules does not apply to these drugs, making it difficult to predict their properties. Advancements in computational modeling are needed to transition from static structures used for traditional small molecule development to conformational stabi-

lization approaches, considering the dynamic nature of ternary complexes.<sup>6</sup>

The diversity of E3 ligase enzymes is a crucial biological feature, highlighting the huge therapeutic potential of utilizing novel ligases beyond CRBN and VHL to mitigate safety and resistance concerns. Expanding the E3 ligase toolbox to identify new ligases with differential expression and/or activity levels in healthy and diseased tissues is an important challenge to mitigate toxicity and the occurrence of resistance mechanisms due to reduced expression levels. Identifying alternative E3 ligase mechanisms therefore enhances the therapeutic potential of developing TPD drugs with improved chemical properties.<sup>7</sup>

### SITESEEKER: LEVERAGING THE EXTENSIVE E3 LANDSCAPE

Our SITESEEKER platform is uniquely positioned to probe the unexplored proteome space within TPD. Approaches to discover ligands with the potential to direct

degradation in a target or tissue specific manner include building of cis-degraders with an E3-recruiting PROTEINi library fused to a reporter protein leading to reporter degradation, or peptide heterobifunctional degraders comprising E3-recruiting PROTEINi libraries linked to a target-binding warhead.

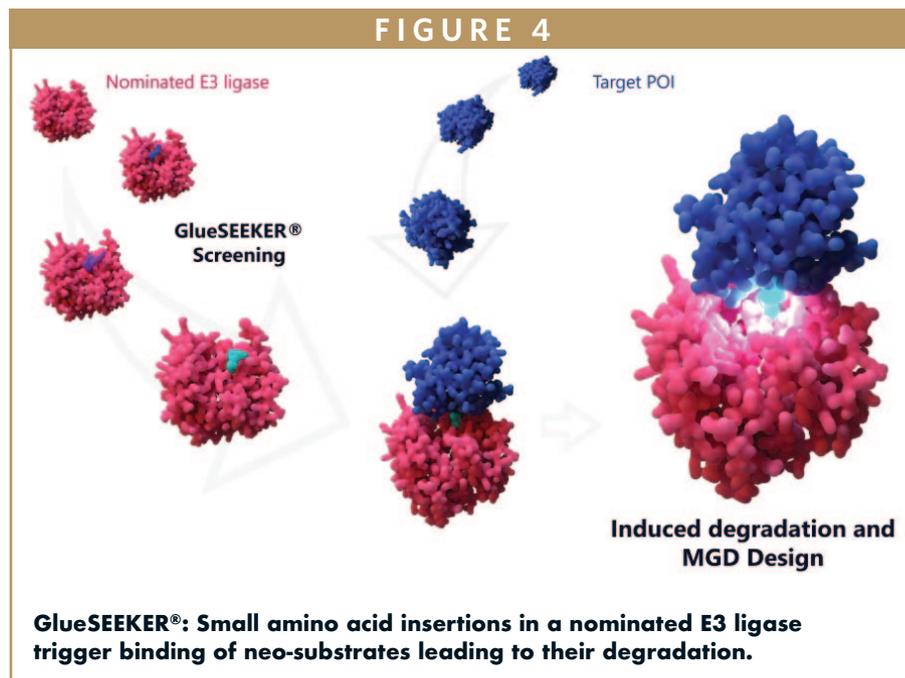
SITeseeker TPD screening campaigns have revealed a host of novel E3s that can be recruited for degradation of therapeutic targets and the PROTEINi degrader motifs able to induce their proximity (Figure 3). These peptide degraders form the basis for design of small molecule heterobifunctional degraders, with the aid of computational modelling.

A number of degraders targeting novel E3 ligases have progressed through drug discovery with successful demonstration of protein degradation, including *in vivo* degradation of the protein of interest in tumor-bearing mice.

The successful development of small molecule degraders directing targeted protein degradation via novel E3 ligases demonstrates the exciting capability of SITeseeker to drive the creation of heterobifunctional degrader therapeutics, expanding the range of therapeutics in the field with the potential to overcome the shortcomings of CRBN-based bivalent degraders.

## GLUESEEKER®: THE NEXT GENERATION OF MOLECULAR GLUE DISCOVERY

Molecular glues have emerged as a promising new strategy for TPD, addressing some of the chemistry challenges associated with bivalent molecules. However, most discoveries in this area have been



serendipitous, such as the IMiDs thalidomide and lenolidomide. Thalidomide's mechanism of action as a molecular glue degrader was discovered when it was found to bind to CRBN promoting the formation of a neomorphic interface for interaction with the neo-substrates Ikaros (IKZF1) and Aiolos (IKZF3), leading to their ubiquitination and degradation.<sup>8</sup> Monovalent degraders, or molecular glues, have smaller molecular sizes than bivalent degraders and function by creating a new interface between the E3 ligase and the protein of interest or neo-substrate. However, innovative approaches are needed to drive the rational design of these molecules. PhoreMost's new GlueSEEKER platform offers a novel method to tackle this challenge and redirect E3 ligases to novel targets.

Key concepts such as protein-protein interfaces and compound-induced proximity are crucial for understanding and characterizing molecular glue interactions. These concepts have helped in rationalizing the design of successful phenotypic screening campaigns. However, computational methods alone are not providing

sufficient sensitivity in identifying interfaces and surface contact points between an E3 ligase and a protein of interest.

GlueSEEKER technology leverages advances in machine-learning and protein structure predictive models to identify novel binding sites within an E3 ligase. This identification permits the insertion of high-complexity libraries of small amino acid sequences that enhance affinity to known targets or induce neomorphic protein-protein interactions (Figure 4). The combination of these tools with high-throughput screening and NGS deconvolution for degradation of the protein of interest in a real biological model offers a great opportunity for molecular glue degrader discovery. The identification of new induced pockets that drive the degradation of a protein of interest is a starting point for the computational design of new molecules that mimic the side-chain interactions found in protein-protein interactions.

## THE FUTURE OF DEGRADER DISCOVERY

The world of degrader drug discovery is rapidly expanding and evolving, providing new promise for disease targets classically considered “undruggable.” PhoreMost’s SITESEEKER technology combines the benefits of high-throughput screening typically associated with genetic perturbation screens with highly translatable output enabling the development of small molecule degraders. The versatility of PROTEINi library design and implementation has not only allowed SITESEEKER to be exploited for the development of heterobifunctional degraders, but has also permitted its adaptation to the discovery of molecular glues.

With the first wave of cereblon-based degraders showing promise in the clinics, there is much anticipation for the impending improvement and expansion of degrader molecules targeting a diverse array of diseases, with recruitment of novel E3 ligases playing a big role in the advancement of these therapeutics. ♦

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## BIOGRAPHIES



**Dr. Alberto Moreno** is Associate Director, SITESEEKER® Screening. He earned his PhD in Biochemistry and Molecular Biology (Madrid) and continued his post-doctoral training in Dundee working in DNA replication and DNA damage. He joined PhoreMost in 2016 as Senior Scientist helping to develop the SITESEEKER platform and running the first ever PROTEINi® screens.



**Dr. Laura Butler** is Associate Director, Target ID & Alliances. She joined PhoreMost as a team leader from Atrin Pharma in 2018, where she was working on novel ATR inhibitors. Prior to this, she completed post-doctoral training at the University of Pennsylvania and Birmingham, UK. At PhoreMost, she leads on the deconvolution of hits to their cognate cellular targets and coordinating alliance relationships across SITESEEKER.

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