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& Delivery

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Injection Devices: Proven Approaches Meet Emerging Innovation



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Editor (Name and complete mailing address)

Cindy H. Dubin - 170 Changebridge Rd. C5-4, Montville, NJ 07045

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Full Name	Complete Mailing Address
Ralph Vitaro	170 Changebridge Rd. C5-4, Montville, NJ 07045
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PUBLISHER/PRESIDENT

Ralph Vitaro - (973)263-5476
rvitaro@drug-dev.com

MANAGING EDITOR

Cindy H. Dubin
cdubin@drug-dev.com

CREATIVE & PUBLISHING DIRECTOR

Shalamar Q. Eagel

CONTROLLER

Debbie Carrillo

CONTRIBUTING EDITOR

Shaukat Ali, PhD

TECHNICAL OPERATIONS

Mark Newland

EDITORIAL SUPPORT

John Roy

DIRECTOR, DIGITAL STRATEGY

Mike Walker

DIRECTOR, TECHNOLOGY & CYBERSECURITY

Stephen Walker

Corporate/Editorial Office

170 Changebridge Road, Suite C5-4, Montville, NJ 07045
Tel: (973) 299-1200
Fax: (973) 299-7937
www.drug-dev.com

Advertising Sales Offices

International Sales Director

Amy Nicklaus
170 Changebridge Road,
Suite C5-4,
Montville, NJ 07045
Tel: (862) 274-5872
Fax: (973) 299-7937
E-mail: anicklaus@drug-dev.com

Global Sales & Marketing Director

John Kiesewetter
P.O. Box 8548
Eugene, OR 97408
Tel: (541) 338-0022
Fax: (541) 338-0044
jkiesewetter@drug-dev.com

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"I believe we are entering an era where intelligent delivery systems will become as important as the drug itself. The convergence of biologics, digital health, connectivity, and closed-loop-controlled delivery has the potential to improve adherence, generate valuable treatment insights, and bring therapies once confined to hospitals and infusion centers directly to patients. Ultimately, success will be measured not by what the device can do, but by what it enables."

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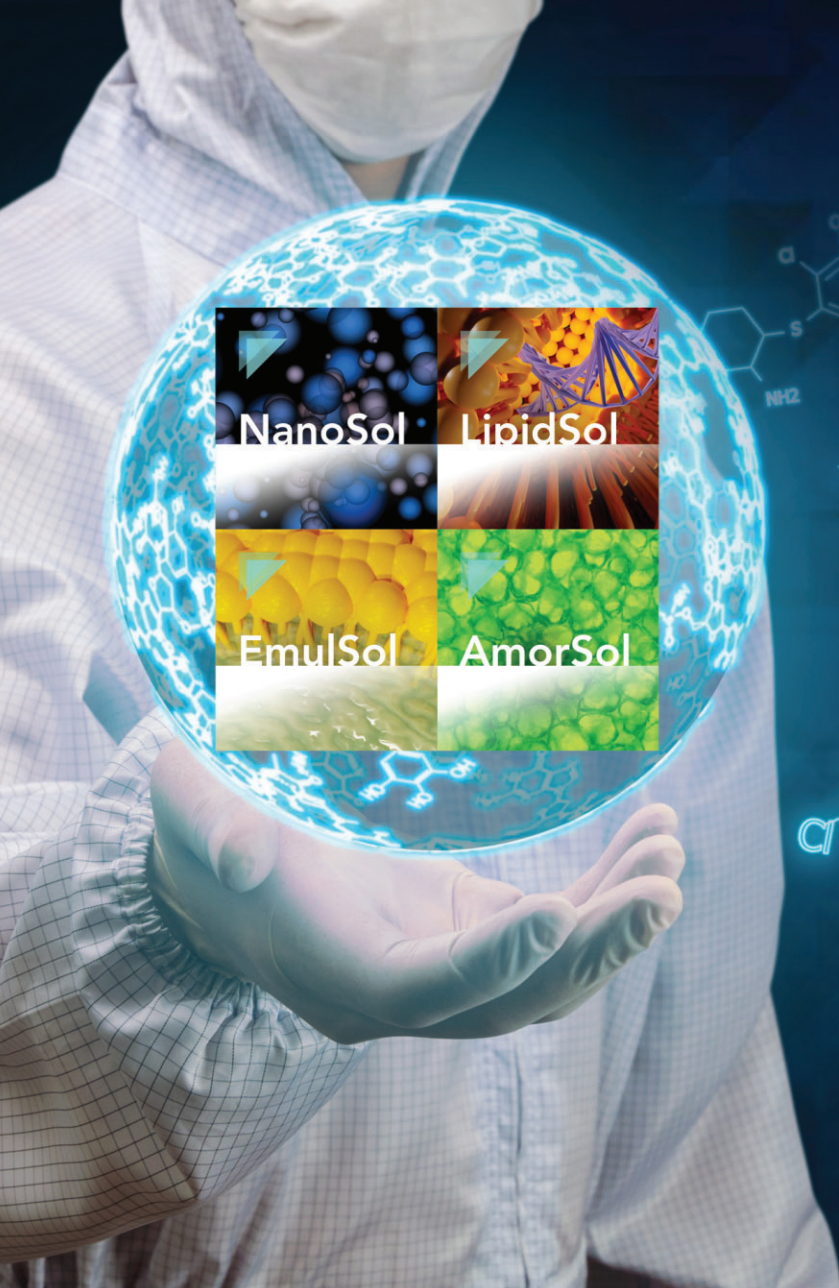
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MARKET NEWS

AND

TRENDS

Early Clinical Trial Evaluating Treatment of Malignant Brain Tumors

Adaptin Bio, Inc., a biotechnology company focused on developing precision cancer therapies with improved delivery to the brain and other tissues, announced today that enrollment has opened for a Phase 1 clinical trial evaluating its proprietary BRiTE (Brain Bispecific T cell Engager) therapeutic, APTN-101, as a treatment for glioblastoma (GBM), the most common and aggressive primary brain tumor. The BRiTE platform was developed by a distinguished team of researchers at Duke University, the study site for the first-in-human clinical trial.

The Phase 1 clinical trial has an open-label, dose-escalation design with the primary objective to evaluate the safety profile and maximum tolerated dose of APTN-101 in patients diagnosed with World Health Organization (WHO) Grade IV Malignant Glioma (GBM that expresses Epidermal Growth Factor Receptor variant III [EGFRvIII]). The study is expected to enroll up to 15 adult patients, and the primary endpoint is the proportion of patients with a dose limiting toxicity observed within each dose level. Secondary endpoints are the pharmacokinetics of APTN-101, and the objective response rate based on modified Response Assessment in Neuro-Oncology Criteria. Exploratory endpoints include an assessment of biological activity as evidenced by changes in cytokine levels, formation of anti-BRiTE antibodies, overall survival and progression free survival.

"Opening enrollment in the Phase 1 trial is an important milestone in the clinical development of APTN-101, a potential best-in-class therapy for the treatment of glioblastoma," said Michael J. Roberts, Ph.D., President and CEO of Adaptin Bio. "In preclinical studies, APTN-101 demonstrated impressive efficacy targeting glioma cells with precision, eliminating some malignant glioma tumors across multiple aggressive disease models. Our proprietary BRiTE technology was developed to enhance APTN-101's ability to cross the blood-brain barrier, to selectively target and then attack glioma tumor cells. We believe this mechanism of action is a significant innovation that provides a key differentiator compared to standard-of-care therapies. Since such standard-of-care therapies (including surgery, radiotherapy and chemotherapy) are not curative, disease recurrence is common. As a result, patients diagnosed with GBM currently have a median

survival of only 12 to 18 months with just 5% of patients surviving beyond five years. Given the promising preclinical data that has been generated for APTN-101 so far, we believe that leveraging the BRiTE technology with APTN-101 has potential to become an important therapeutic option for patients diagnosed with this difficult-to-treat disease."

BRiTE's unique delivery mechanism and mode of action harness the ability of T cells to precisely target and destroy glioma cells while effectively navigating the brain's unique environment. Specifically, APTN-101 is engineered to cross the blood-brain barrier (BBB) to target EGFRvIII, a specific protein linked to aggressive brain tumors. In preclinical studies, APTN-101 demonstrated a greater than 7-fold increase in distribution of the EGFRvIII T-cell engager into the brain compared to the EGFRvIII T-cell engager alone. This resulted in complete eradication of EGFRvIII GBM tumors in 70%-80% of mice. The novel treatment is associated with an excellent safety profile and minimal off-target effects in preclinical models.

"Glioblastoma is a disease with a significant unmet clinical need, limited therapeutic options, and little improvement in outcomes," said Mustafa Khasraw, M.D., professor at Duke University School of Medicine, who led the preclinical development team for APTN-101 and is the principal investigator of the upcoming clinical trial. "By combining immune-based tumor targeting with enhanced delivery to the brain, APTN-101 is designed to address two major challenges in glioblastoma treatment. This first-in-human study is an important step in determining whether this approach can translate into meaningful benefit for patients."

Glioblastoma is one of the most aggressive and deadly forms of brain cancer, accounting for approximately 15,000 new cases per year in the U.S. Secondary malignant brain tumors account for about 200,000 new cases annually. The glioblastoma multiforme treatment market is valued at \$3.02 billion in 2025, and researchers forecast an 8% CAGR over the next five years, reaching \$4.44 billion by 2030, according to Mordor Intelligence. Growing demand for therapies that prolong survival is a top driver of the projected growth.

For more information, visit www.adaptinbio.com.



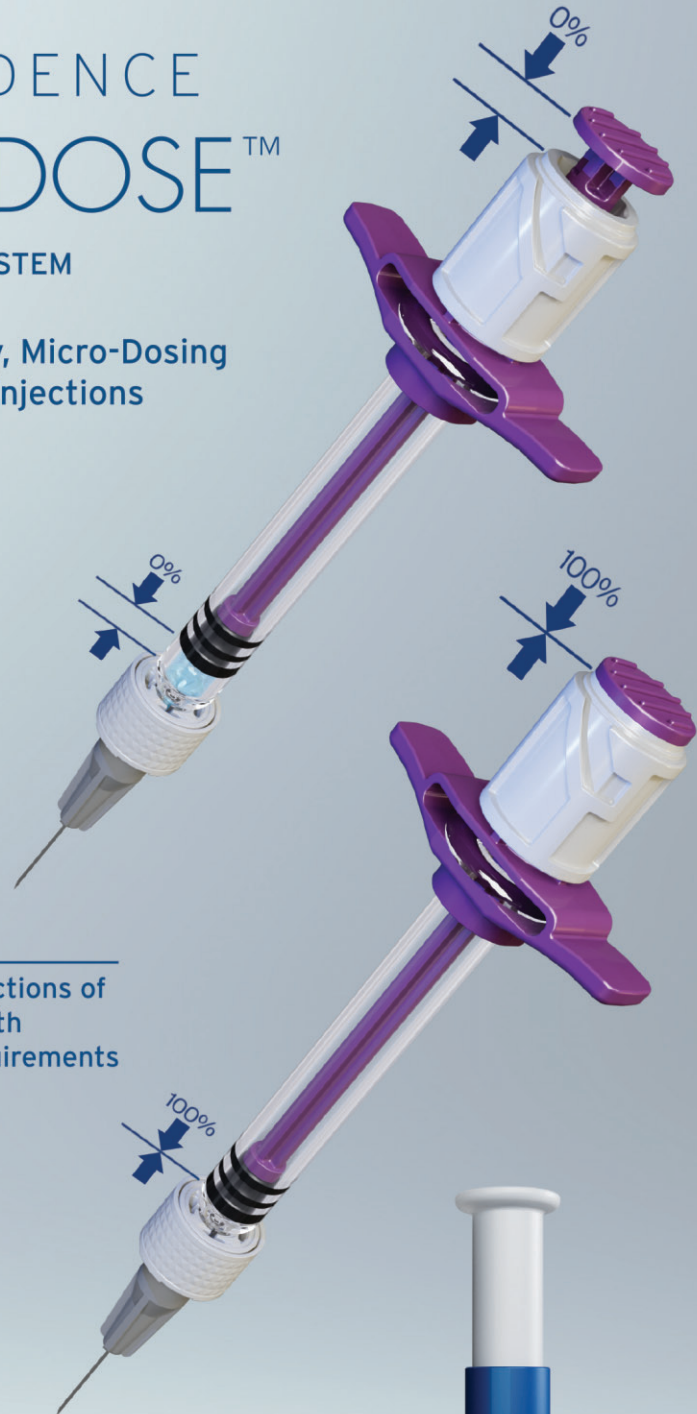
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Novel Series of Small-Molecule Inhibitors Promote Antitumor Immunity

Researchers in Purdue University's College of Pharmacy have developed and validated a novel series of small-molecule inhibitors that promote antitumor immunity and hold promise as novel anticancer agents. The team has developed L-32, a quinolone-based inhibitor shown to reduce tumor growth in vivo and improve upon the potency, selectivity and cellular efficacy of previous derivatives of the inhibitor.

L-32 targets a protein tyrosine phosphatase (PTP) called PTPN22, a negative regulator of the immune system. Team Leader Zhong-Yin Zhang said mutations in PTPN22 are common risk factors for multiple autoimmune disorders, and genetic deletion of PTPN22 leads to robust antitumor immunity.

"Consequently, targeting PTPN22 with small-molecule inhibitors represents an attractive immunotherapeutic strategy to unleash both innate and adaptive immunity against tumor cells," he said.

Zhang said PTPN22 remains underexplored as a therapeutic target despite its known roles in cancer immunity. "This is due to the scarcity of high-quality small-molecule inhibitors," he said. "Consequently, we have advanced a novel paradigm to acquire potent and selective PTP inhibitors by targeting both the active site and its nearby unique pockets."

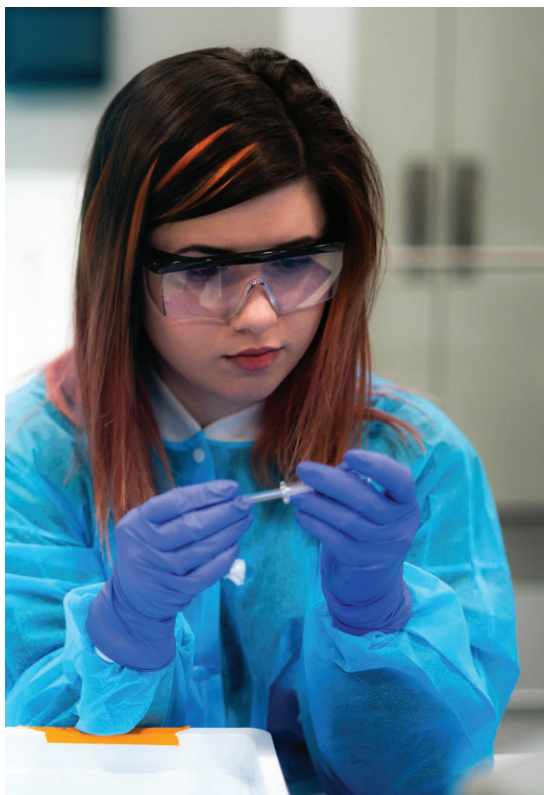
Zhang and his team discovered quinolone-3-carboxylic acid

as a PTPN22 inhibitor from an in-house, druglike small molecule collection. "Using a fragment-based focused library approach by tethering properly functionalized small molecule fragments to the quinolone core, we identified compound L-32, which displays improved potency, selectivity and cellular efficacy compared to previous compounds," he said.

Zhang said L-32 has several advantages over the other compounds, including a more favorable pharmacokinetic profile and drug properties including oral bioavailability. "Importantly, L-32 is superior to early molecules in reducing syngeneic MC38 tumor growth in animal models by promoting robust antitumor immunity, thus offering a promising lead molecule for the development of novel anticancer agents targeting PTPN22," he said.

Zhang said the next steps to further develop the PTPN22-targeting drugs are optimizing L-32 and benchmarking in vivo efficacy. "In particular, we will be expanding the testing for L-32 in more difficult-to-treat cancers including pancreatic and liver cancers, as well as in cancers resistant to current immunotherapies."

Additional information is available at: <https://www.purdue.edu/newsroom/2026/Q3/purdue-small-molecule-inhibitors-shown-to-promote-robust-antitumor-immunity/>.



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Strategic Launch of PEG Powder Portfolio

Indovinya, the global specialty chemicals and surfactants division of Indorama Ventures, announced the strategic launch of its OXIPURITY® 4000 P (Polyethylene Glycols in Powder) portfolio across the Europe, Middle East, and Africa regions. The expansion marks an important step in strengthening the company's footprint in the highly regulated pharmaceutical excipients market in the region.

Designed to meet the stringent requirements of both the European Pharmacopoeia (EP) and the U.S. Pharmacopeia (USP), the OXIPURITY® 4000 P portfolio supports consistent manufacturing performance and high product quality. The introduction of PEG in powder form expands Indovinya's ability to serve solid dosage applications, enabling pharmaceutical companies to optimize their production processes.

"Our OXIPURITY Powder launch is supported by European partners and a dedicated structure of R&D and technical experts, combining deep chemical expertise with functionalities know-how to support customers in developing pharmaceutical products," said Fabiana Marra, Marketing and R&D Director at Indovinya.

The quality of solid dosage forms is closely linked to powder

performance. OXIPURITY® 4000 P has been developed to address key industry needs, including:

- Improved flowability, enabling stable manufacturing speeds and reduced weight variation
- Controlled particle characteristics, supporting better API distribution and formulation consistency
- High regulatory standards, with production aligned to Good Manufacturing Practice (GMP), ensuring safety and traceability across the value chain

Partnering with Indovinya from the early stages of formulation development enables customers to navigate regulatory requirements, optimize product performance, and bring innovative pharmaceutical solutions to market faster.

"Our goal is to simplify both sourcing and formulation through proximity and partnership, offering customers reliable access to high-quality excipients backed by strong technical expertise," Marra added.

More information is available at <https://indovinya.indoramaventures.com/>.

Lonza Launches Rapid Custom Media Prototyping Service

Lonza has announced its Rapid Media Prototyping Service (RaMP), giving biopharmaceutical companies faster access to custom liquid and powder media for screening, process confirmation and early development. With the possibility to send non-GMP powder batches from 1-10 kg and liquid batches from 1-100 L produced within 10 working days, the service helps scientists accelerate timelines, generate critical process data and prepare for GMP manufacturing.

RaMP addresses common early development challenges, including long lead times for custom prototype media, limited small-batch manufacturing options and the need to align early formulation work with future manufacturing requirements.

RaMP is part of Lonza's end-to-end custom media and buffer solutions offering, supporting customers from media development and screening through non-GMP prototyping and commercial GMP manufacturing. By linking early formulation work with long-term scalability, the service helps simplify development and support manufacturing readiness.

Omar Wahab, Vice President, Head of Bioprocessing, Lonza,

commented: "Development teams are under pressure to generate data quickly, make informed process decisions and keep programs moving toward the clinic. RaMP gives customers the possibility of rapid access to custom media in the quantities they need, when they need it. By connecting early screening and process confirmation with future GMP requirements, we help reduce scale-up risk, simplify technology transfer and support a more efficient path to commercialization."

Delivered through Lonza's global media development and manufacturing network, RaMP combines rapid turnaround, flexible batch sizes and specialized expertise to help customers advance development with greater confidence while preparing for scale-up and GMP manufacturing.

Further information about Lonza's custom media capabilities, including development, prototyping and manufacturing support, is available at https://bioscience.lonza.com/lonza_bs/US/en/custom-media-and-buffer-solutions.

FDA Gives Priority Review of NDA for Stargardt Disease Type 1 Treatment

Belite Bio, Inc., a clinical-stage drug development company focused on advancing novel therapeutics targeting degenerative retinal diseases that have significant unmet medical needs, today announced that the U.S. Food and Drug Administration (FDA) has accepted and granted Priority Review designation of the New Drug Application (NDA) for tinlarebant for the treatment of Stargardt Disease Type 1 (STGD1). The FDA has set a Prescription Drug User Fee Act (PDUFA) date of February 12, 2027.

The filing was based on the results from the Phase 3 DRAGON trial, which evaluated tinlarebant for the treatment of STGD1. In the study, tinlarebant demonstrated a statistically significant and clinically meaningful 35.7% reduction in the growth rate of atrophic retinal lesions, measured as definitely decreased autofluorescence (DDAF) by fundus autofluorescence imaging, compared with placebo. Tintlarebant has been generally well tolerated in clinical trials with side effects consistent with its mechanism of action. If approved, tinlarebant would be the first ever FDA-approved treatment option for STGD1, a rare, inherited retinal disease caused by mutations in the ABCA4 gene that leads to progressive and irreversible vision loss and affects an estimated 53,000 people in the U.S. alone.

"The acceptance of our NDA with Priority Review designation underscores the immediate need among the Stargardt disease community for an approved treatment option, and we believe it reinforces the quality and depth of the data that we've generated," said Dr. Tom Lin, Chairman and Chief Executive Officer of Belite Bio. "Stargardt disease typically presents early in life and leads to progressive, irreversible vision loss. We are proud that, if approved, tinlarebant could positively impact the decline in vision that was previously inevitable. We look forward to working with the FDA through its review process and remain focused on our commercial readiness and execution following potential approval."

"The acceptance of our NDA is an important milestone driven by the clinically meaningful results from our Phase 3 DRAGON trial, which showed reduction in atrophic retinal lesion growth rate compared to placebo, supporting tinlarebant's oral, once-daily mechanism," said Dr. Hendrik Scholl, Chief Medical Officer of Belite Bio. "As a practicing physician, I have treated people living with Stargardt disease for more than 20 years and have seen firsthand the challenges that it brings. As of now, the only options that we have to offer people as their blindness progresses are visual aids, further emphasizing the impact that tinlarebant could have on people living with this debilitating disease, if approved. We continue to see enthusiasm across the Stargardt community at the prospect of this potential treatment."

Tintlarebant is a novel oral therapy that is intended to reduce the accumulation of vitamin A-based toxins (known as bisretinoids) that cause retinal disease in Stargardt Disease and also contribute to disease progression in geographic atrophy, or advanced dry age-related macular degeneration (AMD). Bisretinoids are by-products of the visual cycle, which is dependent on the supply of vitamin A (retinol) to the eye. Tintlarebant works by reducing and maintaining levels of serum retinol binding protein 4 (RBP4), the sole carrier protein for retinol transport from the liver to the eye. By modulating the amount of retinol entering the eye, tinlarebant reduces the formation of bisretinoids. Tintlarebant has been granted Breakthrough Therapy Designation, Fast Track Designation, and Rare Pediatric Disease Designation in the U.S., Orphan Drug Designation in the U.S., Europe, Japan, and Switzerland, and Sakigake Designation in Japan for the treatment of Stargardt Disease.

Find more information at <https://belitebio.com/>.

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FORMULATION FORUM

High Concentration Biologics for Injectable Drug Delivery

By: Shaukat Ali, PhD, Sr. Director, Scientific Affairs & Technical Marketing,
and Jim Huang, PhD, Founder & CEO, Ascendia Pharmaceutical Solutions



Shaukat Ali, PhD
sali@ascendicdm.com



Jim Huang, PhD
jhuang@ascendiacdm.com

INTRODUCTION

Continued interest in development of high dose proteins or biologics for injectables has changed the basic understanding of drug delivery.¹ It sounds simple but is complex due to macromolecule irreversible aggregation, increased viscosity, particle formation, long term stability and safety, immunogenicity and efficacy of drug products. Derived from living cells, these biologics or proteins can be used for treatment of a variety of life-threatening diseases because of their specificity to certain target cells. Formulations requiring high dose when often administered intravenously (IV) by dilution are aimed at preventing aggregation of proteins. Higher drug concentrations in an alternative to IV in smaller injection volumes could alleviate injection site pain.² Drug concentration at and above 100 mg/ml is categorized as high dose, whereas, at or above 250 mg/ml is categorized as ultra-high dose with injection volumes of about 2 ml.³ Other factors affecting the high dose proteins, most specifically, include their syringeability and injectability, which are governed by concentration of drugs in certain injection volumes. Determining the optimal dose and volume in early clinical phases is challenging. The high dose and less volumes of proteins/biologics are desired for higher clinical efficacy for treatment of certain disease such as rheumatoid arthritis, psoriasis, and neurological disorders, and preferably administered by subcutaneous (SC) than intramuscular (IM) or IV route of administration, primarily aimed at long term care and life cycle management, and to comply with patient compliance. Ghosh et al cites the number of drugs approved and of them, over 46 high concentration antibodies or biologics, 34 of them approved by subcutaneous (SC), and only 6 by intravenous (IV), and 1 by intramuscular (IM) route of administrations. This article also cites that

majority of them approved as ready to use (RTU) and only 4 are approved as lyophilized drugs.⁴

FORMULATION DEVELOPMENT CHALLENGES WITH HIGH CONCENTRATION BIOLOGICS

High concentrated biologics prone to aggregate which may negatively impact product's quality, safety, stability and efficacy, and also could lead to immunogenicity risk by SC.⁵ These challenges stem from formulation development to analytical and then continue during manufacturing. All these can be addressed by physical characterization tools and analytical methods. For biologics at concentrations 100 mg/ml or higher with limited supply of API, a 2-fold or higher concentrations are attained by centrifugation or diafiltration or tangential flow filtration. Increasing concentrations lead to increased protein-protein interactions, which could impact on conformational and/or colloidal stability and aggregation. Measured by differential scanning calorimetry (DSC) to quantify the free energy difference (ΔG) between natural and denatured proteins, this value dictates the conformational stability; higher ΔG , means greater the stability of proteins or vice versa. Other parameters such as particle size can be measured for colloidal stability by dynamic light and static light scattering. Higher colloidal stability means the proteins maintain stability as a monomer in native state or partially denatured states due to repulsive or electrostatic interaction.²

Analytical challenges require rapid and simultaneous liquid chromatography and mass spectrometry methods for determination of degradants or any other impurities. An understanding of mechanism of proteins and excipients degradation and their interactions in solutions is

equally important for selecting the appropriate bio-analytical methods for determining formulation stability. Polysorbates, for example, are known to form reactive oxygen species, may react with proteins to cause significant degradation. In cases like these, LC-MS could be used to quantify the chemical degradants. Physical degradants like conformational changes, denaturation and protein surface adsorption can also be detected by appropriate techniques including DSC and DLS. Other complementary techniques such as differential scanning fluorometry (DSF) can also be used to understand thermal stability, NMR for structural characterization, FTIR for examining the amide I and II bonds of proteins to probe the secondary structure, while circular dichroism (CD) can be used to understand the secondary and tertiary structures of proteins.⁶

Manufacturing challenges stem from lack of appropriate equipment and/or facility. Therefore, a clear guidance is required for scale up and manufacturing high concentration biologics. For example, vessel size with appropriate shaft or mixer can all play an important role for high concentration formulations. Overly mixing time can increase the chances for degradation of biologics, especially, at higher concentrations. Thus, the real emphasis is to reduce processing time by maximizing flux rates under controlled temperature and pressure to further minimize the risks for potential degradation in either aqueous or non-aqueous manufacturing media.⁶

Processing techniques such as spray drying, solvent extraction, dehydration, the ionic liquids among others are used for manufacturing non-aqueous based suspensions. Spray drying, for example, is applied for creating small spherical fine powder with 5-30 microns in size with the intend to provide better shear thinning and injectability and to protect moisture sensitive

drugs. The dried powder is then suspended in non-aqueous injectable non-aqueous vehicle potentially in high concentrations (100 mg/ml - 250 mg/ml) with desired viscosity (<20 cP or less) to help improve stability by reducing aggregation and minimizing risks for inherent hydrolytic degradation. Low temperature solvent extraction and dehydration technique can be used for thermally labile drugs. This anti-solvent technique results in an amorphous powder following precipitation wherein drug particles are embedded in polymeric matrix, allowing excellent controls over particle size, morphology, and surface characteristics with the abilities to maintain colloidal stability in non-aqueous suspensions. Shire et al developed a low shear high concentrated biologic suspension by particle engineering of a protein for subcutaneous injection through small gauge needle by reducing the injection force.⁷

INJECTABILITY OF HIGH CONCENTRATION BIOLOGICS

Jayaprakash et al. evaluated range of highly viscous liquids using creative ways to reduce 7-fold injection force.⁸ This significant reduction was calculated on buoyancy-driven eccentricity with aim to control the nominal pressure. The authors used these findings to develop a double-barreled syringe to apply for range of high concentration biological injectables. This low-cost injectable technology is ideally suited for highly viscous SC formulations using conventional medical syringes. Usach et al. examined the SC injectables drugs with reference to pain sensation at the injection site.⁹ They proposed that maximum volume of an SC injection is 1.5 ml with exception of no more than 4 ml if necessary as higher volume is typically associated with the injection site pain. Berteau et al. evaluated different viscosity in SC to monitor the pain at injection site and observed

that high viscous liquids with viscosity 15-20 cP caused less pain and were easily tolerated as opposed to those having viscosity 1 cP or 8-10 cP.¹⁰ In another study, Fransson et al. investigated the effect of pH and buffer strength and found that at neutral pH 7 and buffer strength as low as possible, the SC formulation was more tolerated with reduced pain upon injection.¹¹ Phosphate and citrate buffers with concentrations 10 mM and 7.3 mM, respectively, caused less pain at the injection site.⁹ It is, therefore, imperative to maintain pH and buffer strength, and keep low volume when administering SC, especially, for dosing high dose proteins or biologics. Those SC administrations are typically used in 2 ml volume in prefilled syringe (PFS) or autoinjector (AI). Low volume, high dose SC formulation poses some challenges and to overcome those, a few approaches are used including (i) adding viscosity reducing agent to target drug concentrations as low as 100 mg and as high as 250 mg/ml (ii) use novel technologies to deliver the protein concentration as high as 250 mg/ml or higher, and (iii) use a large delivery device with the capabilities to delivery 2 ml to 40 ml volume. In cases where it is critical to achieve the desired relative bioavailability (rBA), a 2 ml PFS or AI is recommended as compared to large volume delivery device, which is needed for high dose to yield low rBA. Higher volumes > 5 ml/min may pose the challenges in SC, for example, with hyaluronan, a highly viscous liquid that breaks down to hyaluronic acid (HA) by rHUPH20. Thus, maintaining the physiological pH and ionic buffer strength plays an important role in development of SC formulations. Table 1 shows a few selected examples out of 46 commercially available high dose antibodies for subcutaneous and intravenous route of administration.³

Currently the SC approved drugs belong to 2 categories: low volume (< 2ml) with rapid injection (0.5 ml/min) and high volume >2 ml)

TABLE 1

Brand Rx	Chemical name	Conc., mg/ml	Dosage form	Indication	pH
Aduhelm®	Aducanumab-avwa	100	Solution	Alzheimer	5.5
Ajovy®	Fremanezumab-vfrm	150	Solution	Migraine	5.5
Benlysta®	Belimumab	200	Solution	Lupus	6
Cimzia®	Certolizumab	200	Lyophilized and Solution	Crohn's disease	5.2
Cosentyx®	Secukinumab	150	Lyophilized	Psoriasis	5.8
Dupixent®	Dupilumab	150-175	Solution	Dermatitis	5.9
Humira®	Adalimumab	100	Solution	Rheumatoid arthritis	5.2
Nucala®	Mepolizumab	100	Lyophilized and Solution	Asthma	6.3-7
Orencia®	Abatacept	125	Solution	Rheumatoid arthritis	6.8-7.4
Repatha®	Evolocumab	120	Solution	Hyperlipidemia	5
Saphnelo® *	Anifrolumab-fnia	150	Solution	Lupus	6
Siliq®	Rodalumab	140	Solution	Psoriasis	4.8
Tremfya®	Guselkumab	100	Solution	Psoriasis	5.8
Vyepti® *	Eptinezumab	100	Solution	Migraine	5.8
Xembify®	Human polyclonal antibody	200	Solution	Immunodeficiency disease	
Xolair®	Omalizumab	125 and 150	Lyophilized and Solution	Asthma	5.5-6.5

* Intravenous

List of Marketed High Concentrate Biologics

with slow injection (< 5 ml/min). Low volume and rapid SC injection meet the patient compliance.

EXCIPIENTS FOR HIGH CONCENTRATION PROTEINS & BIOLOGICS

A number of key ingredients are used to formulate high dose proteins and biologics. Those excipients belonging to different class and type, help stabilize the formulations. These

ingredients are often used to counter the intermolecular interactions arise from van de Waal's forces, hydrogen bonding, hydrophobic and electrostatic forces. Table 2 lists the excipients and their functions. These include amino acid salts like arginine hydrochloride, histidine hydrochloride, lysine hydrochloride, and inorganic salts like sodium chloride, sodium sulfate, sodium acetate and their utilities in reducing the viscosity of high concentration drug products.

Ghosh et al. lists all the excipients with different functionalities.⁴ Citing only those, such

as the tonicity modifiers like sucrose, sodium chloride and others are added to maintain the blood osmolality of 300 mOsm/kg with the optimal osmolality range of isotonic solution not greater than 600 mOsm/kg to prevent pain.⁹ Sucrose is commonly used as a tonicity modifier for 18 out of 46 high concentration marketed biologics. Citing a few examples, Tragarzo® and Vabysmo® both contain sucrose and sodium chloride. There are several examples of marketed drugs containing sucrose, sodium chlorides along with trehalose, and amino acids. Xolair®, Aduhelm®, Evekeza®, for



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TABLE 2

Excipient	Function
Sucrose, trehalose, maltose, sorbitol, mannitol	Conformational stabilizer
Polysorbate 20, Polysorbate 80, Poloxamer 188	Reduce interfacial stress
Arginine, proline, glycine, histidine, methionine, sodium chloride	Buffering agent to stabilize charge interaction, viscosity modifier, tonicity modifier
Methionine	Anti-oxidant
EDTA, DTPA	Chelating agent
Phosphate, acetate, citrate	Buffer, maintains pH

List of Excipients in Formulation of Proteins and Biologics⁴

examples, contain arginine, most commonly amino acid, use as stabilize to prevent aggregation of high concentration biologics. Interestingly, a majority of high concentration approved drugs contain polysorbate 80, 10 contain polysorbate 20, 3 contain poloxamer 188 as solubilizers or stabilizers. On packaging, it's worth noting that majority of the products are approved in the vials except 10 in autoinjectors and 5 in pre-filled syringes.³

NOVEL TECHNOLOGIES FOR HIGH & ULTRA-HIGH CONCENTRATED BIOLOGICS

HILOPRO® technology is used to achieve the drug concentrations as high as 250 mg/ml by reducing the viscosity of mAbs liquid < 20 cP by adding two ingredients, nicotine and tryptophane in 20 mg or less.¹² Comera Life Sciences, for example, utilized caffeine to reduce the viscosity 37 cP or less to achieve the concentration as high as 200 mg/ml of two mAbs: ipilimumab and infliximab.¹³ Avantor used bis acetyl lysine and propionyl serine to reduce viscosity and increase concentration and also to improve shelf life and stability of proteins. Xeris Pharmaceutical utilized its Xeriject spray drying and particle engineering technology to achieve crystalline suspensions

with concentrations as high as 400 mg/ml, while Lindy Biosciences used its particle engineering microclassification technology in organic solvents to achieve spherical dense, stable particles with drug concentrations as high as 300 mg/ml and 600 mg/ml. Elektrofi, on the other hand, used its Electroject technology to achieve the ultra-high drug concentrations; 500 mg/ml and 700 mg/ml as microparticle based suspensions with greater stability by reducing protein-protein interactions and maintaining it injectability. Seran Bio used its proprietary spray drying technology to achieve protein concentrations as high as 400 mg/ml by particle densification to minimize glide force. Jons et al. used novel polyacrylamide-based surfactant in spray drying to increase the glass transition of particles to help improve the mechanical properties for robust suspensions and injection forces for syringeability.¹⁴ ENHANZE®, a subcutaneous proprietary technology by Halozyme, depolymerizes hyaluronan enzyme to improve mobility of protein solutions, thus allowing much greater volumes (ca.5-10 ml) of high concentration therapeutic doses of mAbs including Herceptin Hylecta® (trastuzumab and hyaluronidase, Phesgo® (pertuzumab, trastuzumab and hyaluronidase) among others.¹⁵

IONIC LIQUIDS FOR HIGH CONCENTRATION BIOLOGICS

Since discovery of ethyl ammonium nitrate as IL in 1914 by Paul Walden, ILs have gained universal recognition.¹⁶ Ionic liquids (ILs) are considered environmentally green solvents, derived from salts and exist as liquid at temperature below 100°C. Because of the abilities to dissolve challenging poorly soluble molecules, they have been used in formulation and drug delivery in modern times. Formed by combining the cation and anion entities, ILs are stable, non-flammable and act as non-volatile solvents for dissolving difficult molecules.

ILs utilities in formulation of small and large molecules and biologic are also noteworthy. For instance, ILs have been known to mitigate protein-protein interactions to formulate antibodies at an ultra-high concentration as high as 200 mg/ml with viscosity <20 cP, stable at 37°C, and ideally suited for SC administration leading to improved bioavailability.¹⁷ Since many of the biologics and antibodies are approved at low dose concentrations (cs. 50 mg/ml or less), preferably administered via intravenous infusion, ILs open doors for many biologics requiring high doses with low injection volumes by SC. Zinbryta®, for instance, is approved in

pre-syringe at 150 mg/ml, whereas, Benlysta® is approved at 200 mg/ml in autoinjectors for subcutaneous administration. Higher concentrations can lead to higher viscosities, thus finding a balance to minimize aggregation by decoupling protein-protein interactions, degradation and denaturation is an optimal requirement for manufacturing biologics.¹⁷

Protein aggregation in biologics remains challenging, especially at high concentrations. Those challenges can also be overcome by genetic engineering and/or chemical modification of “aggregation prone” amino acid sequences to alleviate protein-protein interactions. Chemical modifications of biologics through PEGylation, acylation and cyclization have been used to improve stability and help increase immunogenicity and reduce activity. Excipients like sugars, amino acids, solubilizers like polysorbates, are used to protect proteins on storage. ILs offer an exceptional stabilization property by providing a charge shielding effect around drug molecule, thereby, reducing aggregation and denaturation.

Banerjee et al. evaluated CAGE, an IL derived from choline and geranyl acid as salt, in oral insulin formulation and found that it was absorbed through intestinal membrane via modulational of intestinal mucus properties.¹⁹ In another study, Sundaram et al. used ILs derived from choline and amino acids for oral delivery of insulin and found that depending upon concentrations of amino acids used, some amino acids have more profound effect on secondary structure of insulin and other ILs derived from choline-glycine and choline-

alanine formed appreciable amounts of aggregates at high concentrations.²⁰ Tien and Kayser observed that choline-glycine IL at concentration of 10 mM or less, showed highest potential due to enhanced stability while preserving the conformation stability.²¹

Dhiman et al. evaluated an IgG antibody in ILs comprised of choline (Chol) and different counter ions such as acetate (Ac), chloride (Ch), dihydrogen phosphate (Dhp), and found that thermal stability was improved at 0.5-2.5 mM in the order: Chol:Ac > Chol-Ch > Chol-Dhp > IL free.²² Increasing the concentration of Chol-Ac and Chol-Ch increased the melting to 8°C and 80°C, respectively, from 76°C. Long term stability also improved significantly at 2 mM and 2.5 mM of all ILs. Taken collectively, ILs comprised of Cho-Ac and Chol-Ch showed an excellent long-term stability. Reslan et al. examined the stability of trastuzumab 20 mg/ml in an IL comprised of Chol-Dp and compared with Herceptin® at 60 mg/ml at 25%, 40% and 53% of Chol-Dhp comprised of 5.5 mM histidine, 6.4 mM histidine chloride monohydrate, 144 mM trehalose dihydrate and 10 ppm polysorbate 20.²³ In all cases, the thermal stability in Chol-Dhp was significantly greater, and adding the excipient further enhanced the thermal stability.

In a recent study, Alkhawaja et al. investigated atezolizumab (Amab), a highly susceptible antibody prone to aggregation and instability due to lack of an oligosaccharide moiety, at concentrations 300 mg/ml (30%), 500 mg/ml (50%), 700 mg/ml (70%) and 800 mg/ml (80%) in Tris HCl buffer and in ILs each comprised of choline-valine (Chol-Val) and

choline-glycine (Chol-Gly).²⁴ The data suggests that Chol-Val at 30% and 50% stabilized the antibody on incubation over 7 days period as represented by no or insignificant changes in particle size distribution and/or polydispersity index (PDI) but showed a significant degradation at higher concentrations 70% or above. On the other hand, Chol-Gly IL showed much greater colloidal stability of Amab on incubation at concentrations as high as 70% as observed by no change in particle size distribution and/or PDI over 7 days period at room temperature. Tris HCl buffer exhibited a similar colloidal stability as Amab in Chol-Val at concentrations as high as 50% and was independent of temperature.

ASEPTIC SPRAY DRYING FOR HIGH CONCENTRATION BIOLOGICS

Aseptic spray drying can be used to manufacture small and large molecules as well as biologics including vaccines, proteins, peptides, antibiotics for IV, IM and SC dosages. Fast drying with short residence time during process gives an edge to many temperature sensitive molecules like vaccine, proteins and biologics to yield dry powder in aseptic and non-aseptic conditions. Aseptic spray drying was first used in 2006 for Exubera® VR by Pfizer for an insulin inhaled powder. Other examples include Verity Pharmaceutical's triptorelin pamoate (Trelsatar LA) as intramuscular microsphere suspension for prostate cancer, lanreotide acetate (Somatuline LA microspheres by Ipsen, RaplixaVR, a biologic for topical

TABLE 3

Cationic moiety	Anionic moiety
Choline, Alkyl ammonium, 1,3-dialkyl imidazolium, N, N-dialkyl pyrrolidinium	Amino acids, acetate, nitrate, chloride, mesylate, triflate, phosphate, borate

List of Ionic Liquids Derived from Reacting Cation and Anion Moieties¹⁸

formulation by ProFibrix BV and levodopa (Inbrija) by Acorda Therapeutics.²⁵

In aseptic process, the equipment is maintained in sterility with convenient drying throughout the production run. In a recent article, Ali and Huang described the use of aseptic spray drying for production of amorphous solid dispersions for improving the bioavailability of poorly soluble drugs.²⁵ The challenges, however, in aseptic spray drying stems from maintaining the sterilization and product handling (filling vials) during manufacturing in the cleanroom environment (ISO 5, 6 and 7). Furthermore, during aseptic manufacturing the liquids and gas entering and leaving the drying zone must be adequately filtered. This aseptic powder derived from the process, can be conveniently filled and easily scalable as opposed to lyophilized powder filled vials, which is time consuming and costly.

BIOAVAILABILITY OF HIGH DOSE BIOLOGICS

As compared to intravenous (IV) route, the biologics possess lower bioavailability by SC route, stemming from large molecular weight, solubility, pH, aggregation, permeation and poor transport. The multilayered skin comprised of epidermis, dermis and hypodermis provide a barrier to entry of drug molecules in adipose tissues. Lymphatic circulation and systemic circulation both account for bioavailability. Biologics and large molecules with molecular weight 16 kD or larger such as antibodies are absorbed through lymphatic capillaries and those with low molecular weight 1 kD and under, are absorbed by blood capillaries.²⁶ Thus, the rate of absorption through lymphatic systems depends upon concentration, molecular weight, pH, ionic strength, viscosity, hydrophilicity, diffusivity and injection volume. Yang et al. evaluated pharmacokinetic (PK) profile of high concentration antibody at 200 mg/ml crystalline infliximab suspension

comprised of 10% ethanol, 10% PEG 3350, 0.1% polysorbate 80, 50 mM trehalose in 50 mM sodium phosphate buffer at pH7 with viscosity <30 cP and compared with solution in IV solution vs crystalline SC suspension.²⁷ While the C_{max} and AUC_{0-4} were comparable for both IV solution and SC crystalline suspension (95 µg/ml vs 112 µg/ml; and 42.8 mg.h/ml vs. 37.5 mg.h/ml), respectively, terminal half-life ($t_{1/2}$) for suspension was 2-fold higher than solution (779 h vs. 390 h).

SC route is highly patient-centric and can be accommodative by adjusting the dosing at certain sites. For example, with a few exceptions, a delivery rate of 0.5 ml/min in abdomen can be administered for volumes as large as 5 ml or higher. In fact, Mathaes et al. from a study concluded that SC injection volume as high as 5 ml is possible by using special injection technique and devices, especially, for the high dose therapies.²⁸ Increasing concentrations, hydrophobicity of biologics, further increases the risk for precipitation and, hence, yields lower bioavailability. All the uncertainties coupled with lack of a reliable *in vivo* model could lead to poor correlation between human clinical and animal preclinical data due to differences in hypodermic structures, physiology and the extent of catabolism. For instance, SC preclinical data in rats, monkeys and min pigs all lack a good correlation with human clinical bioavailability data.

CONCLUSION & FUTURE PERSPECTIVE

High concentration and low volume injections have been the subject of continued interest to meet the patient compliance. It also brings challenges in developing and dispensing the formulations due to high viscosity, attenuable stability and also ease of manufacturability. The latter could lead to major issues in production for clinical and later in commercialization due

to lack of adequate facility and equipment if it was not tackled in very early stage of development. With some exceptions for high volume SC formulations, the “fit for purpose” reusable syringe or infusion pump can be used in early stage until the drug device combination product ready for clinical stages. There are few tools available to predict the *in vitro* release and stability of biologics. Pion’s SCISSOR (subcutaneous injection site stimulator), for example, can be used in early phase or preclinical stage to assess the risk associated with precipitation and hence the release characteristics of biologics, whereas, the SILCS (site identification by ligand competitive saturation) can be used to understand the excipient interactions and stabilization of biologics. While other tools like spatial charge map (SCM), a silico-based model can identify the high viscous polymers by computing the electrostatic charges around the biologic surface, mAb aggregation prediction tool (MAPT) can predict charge aggregation as function of pH.³ Prefilled syringe and cartridge with dual chambers enable reconstitution of lyophilized biologics with the diluent to enhance stability and shelf life. These innovative tools are as important as the regulatory guidelines for developing right devices, packaging and needles with relatively larger gauges (23-26) for efficient delivery of high viscous formulations. All these basic understandings are important to improve patient safety and compliance for treatment of chronic diseases and life cycle management.

Ascendia with its expertise in high concentration and high viscous formulations (solutions and suspensions) of small and large molecules and biologics and with its state-of-the-art manufacturing facility equipped with fill finish capabilities of vials, prefilled syringe and cartridges, can help expedite the development in the clinical stages of drug products in the ISO 5, 6 and 7 (Grade A, B and C) clean rooms. Biologic therapeutics, for example,



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risankizumab (Skyrizi®), first developed in prefilled syringe (90 mg/ml) and later launched in an autoinjector cartridge (150 mg/ml) in conventional excipients or novel ionic liquids, can be manufactured by Ascendia's aseptic process to fill high concentration liquids in vials, prefilled syringes and cartridges using peristaltic and piston pumps. Ascendia with its aseptic spray drying capabilities, can help expedite the development of small and large molecules, and high concentration proteins and biologics in ready to use vials in ISO cleanrooms. ♦

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Amy Nicklaus: 862-274-5872
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ARTIFICIAL INTELLIGENCE

AI/ML Supporting Biomarker & Target Discovery

By: William Whitford

INTRODUCTION

There is rapid and successful development of Artificial Intelligence (AI) and Machine Learning (ML) applications in medicine, including in such fields as pharmacology, drug discovery, and bioinformatics.¹ In this, AI/ML is revolutionizing biomarker and therapeutic target discovery by providing new capabilities, expediting processes, and enabling more informed decisions.

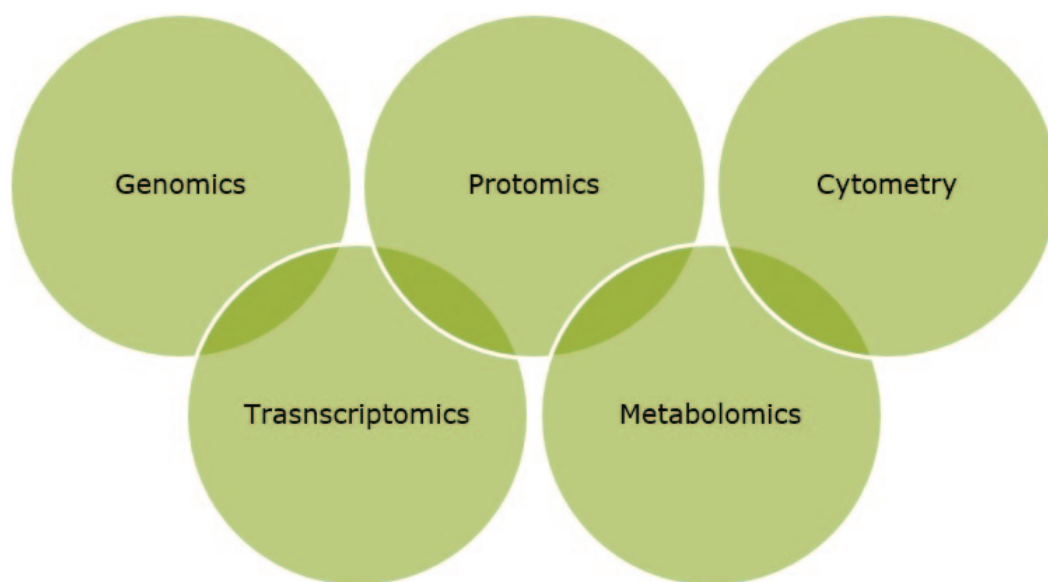
Due to the successful implementation of the digital transformation in biomarker and disease target (BMDT) discovery, data are now routinely captured and distributed in electronic format. AI supports development of tools that function without explicit (deterministic) programming. These (stoichiometric) tools are in-

creasingly used in curating and analyzing data, developing understandings, advising in decisions, and even autonomous agency.

AI/ML provides new capabilities in analysing the rapidly increasing type and amount of biological data employed in identifying potential BMDTs. It can mine research publications and digital libraries to discover and characterize biomolecules or constructs associated with diseases. Its ability to provide deep understanding of relationships is helping in the related disciplines of disease biomarker and therapeutic target investigation and validation.²

Diagnostic, staging, and prognostic biomarkers arise from a broad range of phenomena indicating what is happening in a cell culture or patient. They are objective measurements of cellu-

FIGURE 1



AI is powerful in the discovery of biomarkers and therapy targets using multivariate analysis of DNA, RNA, protein, metabolite, and cytometric data.

AI explores higher-order, multiparametric data from many disciplines.

lar, tissue, or organ activity used to measure the presence, state, or progress of disease. Biomarkers improve patient care by enabling earlier diagnosis, more accurate treatment selection, and improved monitoring of disease progression and therapy response.

An example classical biomarker is HbA1c, used to assess long-term glucose control in diabetics. A newer biomarker involves the BRCA1 and BRCA2 gene mutations, which indicate an increased risk of some hereditary cancers.

Biomarker research is constantly evolving, and new biomarkers are being discovered through analysis of bodily tissue, cell, or fluids using such methods as genome-wide association analysis powered by next-generation sequencing and mass spectrometry-based proteomics, as well as by such imaging techniques as MRI and PET.

A therapy target is also a molecule or system in the body directly associated with a particular disease, but one that can be modulated by a therapy. Target identification is increasingly important in therapy discovery following innovations in assay and experimental technologies. But the recent power provided by AI in the newer multiomic studies is promising even more significant gains (Figure 1).

An example of contemporary targets are the mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene in patients with cystic fibrosis. The primary gene therapy approach here is to introduce a functional copy of the CFTR gene into patient’s cells.

In personalized medicine, AI can analyze demographic or individual patient biology in the context of published research and diagnostic data to help identify suitable BMDT for specific populations or even patients. This, along with AI-enabled

TABLE 1	
Causality Detection	Discovers unknown interactions by identifying dependent and/or independent variables, as well as hidden dependencies.
Data Comparison	Compares simultaneous and parallel data from multiple active moieties or components in both time-series and event data sets.
Dimensional Reduction	Dimensional reduction transforms a number of possibly correlated variables into a smaller number of uncorrelated variables, simplifying complexity while retaining patterns.
Dimensional Analysis	Analysis of the relationships between different objects by identifying their essential features and tracking these dimensions as it places new data in an appropriate dimension.
Pattern Recognition	Identifying specific behaviors or motifs over large amounts of data. By establishing a smaller dataset as a model, it finds similar patterns along the full sequence of information.
Target Prediction	Calculating the most suitable values for the target variables based on inputs from the modelled predictor parameters.
Clustering and classification	Both supervised and unsupervised algorithms reveal groups in datasets by calculating distances in a multidimensional space.
AI systems used in biomarker/target discovery.	

meta-analysis of a candidate therapy’s published primary and off-target activity, can be used to map its overall biological activity, suggesting treatment effects and clinical outcomes.

AI IN BIOMARKER/TARGET DISCOVERY & ANALYSIS

A tremendous amount and type of data is generated in analysing the multiple chemical, physicochemical, and biological systems associated with discovering a candidate biomarker or pursuing its correlation with disease. In target optimization, similar data aids in the identification of both novel therapeutic targets in particular disease, as well as in predicting new targets for existing drugs.

The number of approaches employing such tools as high-throughput screening (HTS) high-content analysis (HCA) is large and growing. While they have already significantly contributed to the field of omics-based biomarker discovery, AI methods are improving their utility and potential.³

AI algorithms help identify candidates due to their ability to handle such large amounts of disparate data, identify patterns, and make classifications or predictions from them.⁴ These algorithms transform previous biased, slow, computer-assisted but human-based approaches to classifications and predictions into fast and objective systems (Table 1).

Due to the many factors involved, AI has demonstrated unique value in characterizing a biomolecule’s potential value in reporting on a disease. AI models correlate data from a BMDT candidate’s measured genotype or phenotype properties to the desired ideal properties and predict its value or even suggest alternatives. Dynamic *in silico* modelling using machine learning and deep learning algorithms are used to model cell and vesicle surface properties, activities, interactions, as well as a drug candidate’s potential disease modulating effects. The power of this related activity is demonstrated by Insilico Medicine in its Phase 2 clinical trial of its AI-discovered drug, INS018055.⁵

Automated and high-throughput technologies generate measurements for

numerous variables across thousands of experimental samples. Because biological systems are inherently interconnected, these data are typically correlated, multi-parametric, and often high-dimensional. Historically, however, such datasets have not always been analyzed in a manner consistent with their complexity. Accurate interpretation increasingly depends upon multivariate analysis (MVA), which examines relationships among multiple variables simultaneously rather than in isolation.

AI-enabled MVA extends these capabilities by identifying nonlinear, higher-order interactions, latent structures, feedback mechanisms, and dependencies that are difficult or impossible to detect using traditional statistical approaches. This is particularly important in complex biological systems that are both dynamic and dynamical, where responses evolve over time and arise from interacting mechanisms that continuously influence one another. Such systems are frequently non-stationary, with relationships among variables changing across developmental stages, physiological states, or environmental conditions. AI methods can model these complex behaviors, integrate heterogeneous data sources, and distinguish meaningful biological signals from noise.

Supported by modern computing and cloud-based infrastructures, AI-powered MVA provides timely predictions, deeper process understanding, and actionable recommendations. By revealing the interconnected factors that govern biological performance, it enables more accurate interpretation and improved decision-making."

Examples of this power in currently available drug discovery tools include an open access machine learning program called ConPlex, developed by researchers

at MIT, which predicts drug-target interactions. ConPlex requires only the sequences of the system's proteins and simple descriptions of the candidate drugs.⁶ AI-Bind is a model that combines network-based sampling with unsupervised pre-training to improve binding predictions for novel proteins and ligands. It is a deep learning drug/target combination identification algorithm with promise in drug discovery.⁷

AI is also being exploited in the emerging field of chemoinformatics. Neural networks have been used in *in silico* screening through chemical modelling for years. However, we are now seeing that synthetic chemistry and chemoinformatics, based upon the application of AI techniques, is promising more powerful analysis, including employing virtual libraries representing a much larger chemical space.⁸ ML models can now predict the properties of new compounds by employing both measured features of the chemical as well as purely theoretical descriptors derived from its chemical graph (a graph-theoretical representation of a molecule) or 3D structure data.⁹

EXAMPLE OF AI VALUE IN BIOPHARMACEUTICAL DISCOVERY

We have seen how AI-empowered AlphaFold can predict protein structures from amino-acid sequences. This success has created hope that these neural networks, trained upon well characterized protein sequences and structures, could also help to create novel proteins with understood functionality. The activity of immunogens, receptor traps, and enzymes are often mediated by a small number of functional residues, with their domains

properly presented by the overall protein structure.

Open AI's GPT4 is an AI generative network we are all familiar with, and this type of AI application is now demonstrating the ability to design therapeutically functional proteins from simple molecular specifications. For example, we are seeing the design of novel protein structures containing prespecified functional sites, in an effective orientation, customized for a particular use or disease therapy.¹⁰

AI techniques enabled researchers at University of California, San Francisco (UCSF) in collaboration with a team at IBM Research, to expand CAR T technology, and make their design more quantitative and predictive. Using neural networks trained to decode combinatorial CAR signalling motifs they discovered key design rules of the system. AI tools working on libraries supported the engineering of receptors with desired phenotypes.¹¹

ProSurfScan is a popular and commercially available program to model the compatibility and binding mode of a candidate on different regions of a protein surface.¹² Here, the protein surface is represented as a graph of nodes defining local supra-molecular interaction (non-ionic binding) features. Convolutional neural networks can then agnostically estimate candidate interactions with distinct regions on the protein surface.

EMERGING THERAPEUTIC MODALITIES & TECHNOLOGIES

We are seeing a remarkable number of emerging developments in the nature of ATMP therapeutic entities, the means to deliver them, and the technologies employed in their production. AI is becoming

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essential in handling the amount and type of data coming from the many high-throughput and high-density analytics and screenings employed here.¹³

Deep learning algorithms such as recurrent neural networks (RNNs) are well-suited for analyzing such massive amounts of multivariate time-series data. They assist in tracking of changes over time from assays of cell type-specific responses, including the expression of specific genes from cultures cells and biobank submissions.

AI's deep learning is supporting a high-level analysis of cell motion, microfluidics, and multiomics. New single-cell analysis techniques allows the study of individual cells' behavior and omics, leading to a deeper understanding of cellular heterogeneity and disease mechanisms. Here, AI is providing the point-to-point analysis of hundreds of individual cells and yields much deeper knowledge than the results of the averages of millions of cells.

Recently, improvements in single-cell whole-genome sequencing is showing promise in tumors that display a mosaic of genetic variation, or sub-clonal mutations that make the tumor more aggressive.¹⁴ One can only imagine the understandings to be revealed as AI classifiers are applied to this data.

There are many other AI-powered applications aiding in therapeutic candidate and BMDT understanding, such as virtual reality (VR) and augmented reality (AR). These are allowing us to visualize and even interact with complex biological structures and datasets. Such capability was reviewed in a Computer Vision and Pattern Recognition Conference which occurred in Vancouver.¹⁵

Finally, it is valuable to realize that AI

supports not only new, previously impossible, capabilities, but can radically speed-up existing data processing activities and applications. For example, AI-driven natural language processing (NLP) does not really change the nature of literature review, but significantly reduces the time involved in examining and summarizing vast amounts of research and medical literature.

EMPLOYING EVIDENCE-BASED ASSOCIATIONS

By examining the structural, biological, or functional similarity of BMDT in diseases of related ontology, AI-based systems can identify candidates with appropriate genetic, biological pathway, or cellular activity. Existing approved disease modulators can provide data valuable in understanding properties or activity in other disease etologies.

Such use of disease ontology requires an understanding of genetic and clinical data, as well as symptoms through evidence-based associations. A new initiative, The Disease Ontology, promises an open-source tool for the integration of biomedical data associated with human disease, disease features, and mechanisms. It hopes to serve as a reference framework for multiscale biomedical data integration and analysis towards strengthening the disease information ecosystem.¹⁶

Existing therapies will have immense amounts of research, clinical, and incremental post-launch data. Such data can reveal much about the nature and associations of a disease with respective phenotype, environment, and genetics. AI can efficiently enable comprehensive multi-parametric collection and analysis of enor-

mous sets of emerging research data with the vast biomedical literature, clinical trial data, electronic health records, and other sources to identify potential BMDT and therapeutic candidates.

The discovery and analysis of various real-world patient data, including published off-label use, is used in the evaluation of the value of proposed BMDT in identified patient populations and even personalized medicine. By searching through historical data pointing out the many primary and off-target clinical effects of a drug, AI can predict candidates in the context of complex endocrine, immune, or metabolic pathways. AI models of the complex interaction networks of existing therapeutic entities with novel candidate BMDT and disease modulators aids in better understanding the relationships between them.

SUPPORT OF TESTING PHASES & CLINICAL TRIALS

Beyond relevant power in data governance and processing, AI's power in clinical trials per se has been well reported, and examples here include more objective and less biased patient recruitment, trial design optimization, regulatory compliance, and data security. Well-fed AI models help researchers to prioritize and design preliminary studies for these candidates and predict the potential efficacy of biomarker candidates in clinical trials.

Trials can produce diverse data types from researchers, program administrators, and clinicians. Such varied sources provide such data types as labelled and unlabelled, structured and unstructured, numerical and categorical, time series, and



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text. AI is extremely powerful in aiding in the collection, transmission, and curation of such disparate data types.

CHALLENGES

Some AI algorithms lack of transparency (“black boxes”) makes it all the more difficult to know whether a system is fair, accurate, and complete. An AI system can also be inappropriate based on flawed assumptions about its application context, users, or their current needs and procedures. AI has been reported to contribute to increased cybersecurity risks— on the other hand, it’s been shown to empower a path to enhanced security.

Explainability and transparency in algorithms and their updates is desired to ensure accuracy and compliance in outputs — yet remains difficult to achieve. Collaboration between domain experts, data scientists, and software testers is crucial to establish and maintain the quality, reliability, safety, and alignment of AI systems throughout the entire product lifecycle.¹⁷

The dynamic nature of AI models, as well as drift in both the real-world scenarios and user behavior, establish a requirement for continued process monitoring and data or model updating. That this is a developing field can result in ambiguity in user terminology, expectations, and implementations — as well as in model aligned behavior and results.

The growing size and complexity of systems is increasing the difficulty in identifying critical functionalities, defining appropriate testing, and establishing acceptance criteria. SaaS, risk-based validation, CSA, and Pharma 4.0 initiatives determined a significant change in validation requirements and solutions — and now the unique aspects of AI we have

mentioned have furthered this need for development in validation approaches.

Deploying AI in compliant environments is a two-edged sword: while it helps ensure such factors as data integrity and increased productivity, questions remain in such topics as how much external information is used in computing results, how much human involvement is necessary for operation, and what the acceptable degrees of algorithm opacity might be. To address this, many authoritative publications are appearing, such as a draft guidance from the FDA¹⁸ and a set of principles from the EMA.¹⁹

Many have remarked that generating sufficient AI-quality data is the greatest limitation to progress in many applications. And, that we need better orchestration of data generation, capture, storage, and processing. Automated system outcomes can be harmed by data that is flawed, mislabelled, skewed, or unrepresentative — or that incorporates historical bias, or other types of errors.

A PROMISING FUTURE

The combination of modern data science, power computing, system connectivity, and AI is creating a sea-change in our capabilities in therapeutic biomarker and target discovery, development, and testing. Some believe the integration of AI in pharma-related the systems will be more transformative than any other emerging technology. ♦

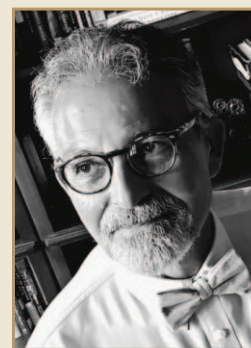
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BIOGRAPHY



William Whitford has over 20 years of experience in biotechnology product and process development. He now publishes oral papers, journal articles, and book chapters on such topics as ATMP, AI/ML applications, and environmentally sustainable biomanufacturing practices. He also enjoys serving on a number of biotechnology committees, boards, and panels, such as the *MagBIO* research consortium *Industry Advisory Board*.

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PLATFORM TECHNOLOGY

How a Novel Immunotherapy Platform is Unlocking the Cancer-Fighting Potential of Unconventional T Cells

By: Michal Sheleg, PhD

INTRODUCTION

For many decades, two mainstays in effective cancer treatment were chemotherapy and radiation, which destroyed healthy cells alongside cancerous ones. Additionally, they often cause severe side effects and lead to resistance or recurrence of the disease.

However, we've recently begun seeing a paradigm shift in the way we treat cancer. Instead of or in addition to directly destroying cancer cells by chemotherapy or radiation, we can induce an effective immune response against cancer cells by immune checkpoint blockers, antibody-drug conjugates (ADCs), chimeric antigen receptor (CAR)-T and other cell therapies.

When the first autologous chimeric antigen receptor (CAR)-T cell therapy was approved by the U.S. Food and Drug Administration in 2017, it generated immense excitement in that this new, personalized treatment approach preserved healthy cells in an individual while mostly targeting those carrying cancer.

However, the cutting edge of cancer research is now expanding beyond conventional T cells to a less-explored, unconventional, unique subset of T cell: mucosal-associated invariant T (MAIT) cells. Just as CAR-T therapies have revolutionized treatments for blood cancers, so engineered MAIT cells may stand to change future allogeneic treatments for solid tumors.

Early research on MAIT cells is displaying some promising signs in their ability to fight cancer, especially by turning to an untapped source of MAIT cells: human placentas.

MAIT CELLS: AN UNCONVENTIONAL T-CELL

In recent years, immunologists have become increasingly interested in MAIT cells. As their name implies, they primarily localize to mucosa-rich regions of the body. MAIT cells differ from conventional T cells by their semi-invariant T-cell receptors (TCRs), which recognize metabolites of vitamin B2 (riboflavin) produced by bacteria and fungi and presented on infected cells.

As a result, MAIT cells are vital in the immune response to infection, protecting organs against external microbial threats.¹ MAIT cells also play a role in tissue repair (wound healing) in healthy and pathogenic conditions, although the precise mechanism of this role is unclear.²

With respect to cancer, MAIT cell's ability to produce type 1 cytokines and exert cytotoxic effects suggests their potential for anti-tumor functions. Furthermore, their distinctive expression of chemokine receptors and their localization primarily in tissues suggests their potential to migrate into solid tumors. However, despite their significant promise in cancer treatment, there are limited reports focusing on their therapeutic application in this context.³

CAR-T therapy represents a highly promising field in cancer research. Significant progress has been achieved in hematological malignancies. However, these successes have not extended to solid tumors. As a result, researchers are seeking alternate options for targeting solid tumors, including allogeneic products and the use of superior T cells, thus turning their attention to MAIT cells.

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Research has uncovered evidence of MAIT cells' work in targeting cancer. For example, one study looked at how circulating MAIT cells helped identify patients responding to anti-PD-1 therapy to treat metastatic melanoma.⁴ Responses to this treatment are highly variable, so researchers are urgently working to identify biomarkers that show which patients may benefit from such therapies.

This study found that the proportions of activated and proliferating MAIT cells and CD8+ T cells were significantly higher and that MAIT cells displayed enhanced expression of genes related to immune activation and effector functions in patients responding to anti-PD-1 therapies, both before they started the therapy and throughout the duration of it. Additionally, researchers found that patients with more than 1.7 percent of MAIT cells among their peripheral CD8+ population displayed an even better response to anti-PD-1 therapy.

Another study found similar results in patients receiving immunotherapy to treat non-small cell lung cancer (NSCLC).⁵ Many patients with this type of cancer do not respond to immune-checkpoint inhibitors.

The study found an increased number of MAIT cells in the tumors of NSCLC pa-

tients that had migrated from the peripheral blood via the CCR6-CCL20 axis. Researchers also found circulating MAIT cells to offer predictive value in whether anti-PD-1 immunotherapy may work in NSCLC patients.

Beyond MAIT cells found in peripheral tissues, research done by Pluri and others has indicated that placentas are rich in highly potent, allogeneic, MAIT cells. These placental MAIT cells exhibit inherent biological advantages that could be pivotal in developing effective treatments for difficult-to-treat cancers, especially solid tumors.

COMBATING GRAFT-VS-HOST DISEASE

Allogeneic CAR-T products offer numerous advantages, but they also present a significant challenge: the risk of graft-versus-host disease (GvHD). This complication arises when donor CAR-T cells perceive the recipient's tissues as foreign and launch an immune attack against them. To date, GvHD remains a barrier to developing an allogeneic cell-based immunotherapy platform.

To address this issue, companies are employing genetic manipulation tech-

niques such as disrupting the native T-cell receptor (TCR).^{6,7} This modification aims to diminish the T cells' ability to recognize and react to host tissues, thereby reducing the likelihood of GvHD.⁸

In contrast, MAIT cells possess a unique TCR that inherently eliminates the risk of GvHD. This characteristic allows them to be scaled from a single donor and used across diverse patient populations.

According to Pluri's data, placental MAIT cells exhibit a lower alloreactivity profile. This reduced alloreactivity suggests that MAIT cells may persist longer in the body, potentially enhancing their therapeutic effectiveness.

While research into placenta-derived MAIT cells is in the early stages, their reduced alloreactivity and potential tumor-fighting characteristics suggest significant potential in treating solid tumors.

ADDRESSING SCALABILITY CHALLENGES WITH ALLOGENEIC SOLUTIONS

While CAR-T therapy has improved outcomes for many patients worldwide, it relies on harvesting cells from the patient's own body for their personal use. Therefore, it can treat only one patient at a time.⁹

Certainly, oncologists and institutions are increasingly adept at initiating treatment, but there remain challenges with autologous treatments. First, it's difficult to isolate enough cells from the sick patient, and any patient-derived cells that are isolated are typically of low quality.

The logistics challenges with autologous therapies are also extremely complex, requiring careful timing at the hospital and manufacturing site.¹⁰ Fur-

ther, it can also be expensive in that it requires specialized laboratories to meet the needs of local patients.¹¹

The autologous nature of CAR T-cell therapy, requiring highly individualized and intricate cell processing, which are major impediments to broader clinical adoption, underscores the need for off-the-shelf approaches that can be used across patient populations — hence, the appeal of allogeneic placental MAIT cells, provided they can be scaled up for practical use.

Although MAIT cells can be found in a frequency of up to 10 percent of CD3+ T cells in human blood, MAIT cells are known to have limited potential for expansion. To solve this problem, Pluri invented a technique that improved the MAIT isolation method from the placenta, thereby increasing the availability of MAIT cells threefold.

The now-patented method not only retrieves MAIT cells but activates them in a better way and increases their growth potential.¹² As a result, Pluri's 3D cell expansion technology potentially represents the needs of many patients per batch.

Traditional suspension bioreactors leave the cells inside susceptible to damaging shear forces, damaging the quality of those cells. Pluri's novel cell-expansion technology ensures that the immune cells produced by the process retain their integrity, functionality, and therapeutic efficacy by using a packed-bed system and a natural scaffolding process that represents a paradigm shift in immune cell expansion. It creates an environment akin to a natural lymph node.

The PluriMatrix is built on the company's platform 3D cell-expansion technology, enabling industrial-scale production of cell-based products via a



packed-bed system design. Cells expand as tissue on scaffolds, which increases the available surface area and provides a uniquely effective growth environment. The cells can either be harvested as single cells or used with the scaffolds as entire tissue.

This approach also reduces the otherwise-complex manufacturing process and high costs associated with autologous CAR-T cell-therapy products. The three-dimensional system and method for culturing and then activating immune cells on a large scale supports the creation of new, innovative allogeneic products in a tightly controlled, fully automated, scalable, and efficient manner.

SUMMARY & FUTURE PERSPECTIVES

While CAR-T and other therapies producing an immune response have revolutionized treatments for blood cancers, therapies targeting solid tumors remain a challenge, despite one recent FDA approval in melanoma.¹³ Placenta-derived MAIT cells offer the potential for significant breakthroughs because of their apparent proclivity for navigating the complex environment for solid tumors.

An allogeneic platform that uses readily available donated cells from human placentas could create a cost-effective, off-the-shelf therapy for solid tumors with the potential to revolutionize cancer treatment around the globe. Combining that allogeneic platform with the latest cell-expansion technology is the key to making these treatments available to many more patients than current treatments are accessible to. ♦

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BIOGRAPHY



Dr. Michal Sheleg is VP of Clinical Development, Pluri, oversees clinical programs and regulatory strategy. She previously served as Pluri's Medical Director. Dr. Sheleg earned her PhD in Toxicology from the Rutgers University/University of Medicine and Dentistry of New Jersey.

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BIOPHARMA MARKET LAUNCH

De-risking Global Market Entry Through Redundant Capacity & Flexible Manufacturing

By: John Ward and Paul Hamill

INTRODUCTION

Developing a new biopharmaceutical can take more than a decade of research and costs billions of dollars in development and clinical trials.¹ Because patent protection is typically sought at the point of discovery, this prolonged development cycle significantly compresses the commercial window available to recoup these investments. By the time a drug is approved, loss of exclusivity timelines are already fast approaching.

Between 2025 and 2030, over \$300 billion in prescription drug revenues are expected to lose exclusivity.² To optimize returns within this compressed timeframe, some sponsors prioritize earlier multi-market launch planning as part of their commercialization strategy. Consequently, launch readiness matters just as much as development progress. For many programs, global expansion is therefore shifting from a long-term ambition to a near-term priority.

This article examines this trend, and also explores how globally integrated contract development and manufacturing organizations (CDMOs) are reducing market-entry risk through redundant capacity and agile downstream execution.

MARKET TRENDS CONSTRAINING MULTI-MARKET LAUNCHES

Achieving an earlier multi-market launch is increasingly difficult due to a convergence of industry trends. Sponsors encounter significant friction caused by constrained manufacturing capacity, complex regional logistics and a tendency to underestimate the final stages of product assembly.

- **High-volume demand is altering what capacity gets prioritized**

The pharmaceutical industry overwhelmingly prioritizes sustained, high-volume manufacturing runs, with large CDMOs building their facilities to minimize equipment downtime. Setting up a production line requires significant time – up to four weeks – and resources, making it commercially unviable to execute frequent equipment changeovers for a run that might only last a few minutes. That bias has become more pronounced for high-demand therapies, such as glucagon-like peptide-1 (GLP-1) medications, and many CDMOs are placing greater emphasis on these large, continuous campaigns.^{3,4}

The impact of this high-volume demand shows up in the middle of the market. Small and mid-volume programs find it harder to secure dependable downstream partners that support a faster speed to market, even when they have a clear regulatory path and a realistic forecast. That “underserved” band spans roughly 10,000 to 5 million units, which is substantial in operational terms but remains deprioritized relative to continuous blockbuster campaigns with runs of tens or hundreds of millions of units.

- **Working in the European market introduces logistical hurdles**

Market requirements can multiply downstream complexity and impact launch timelines, even when demand forecasts are stable. The European Union has 24 official languages before local market preferences are even considered.⁵ This language variation, combined with national regulations, leads to stock-keeping unit (SKU) proliferation. Commercial packaging volumes

then need to be split into multiple smaller, localized variants to meet the sponsor's specific rollout strategy. This fragmentation transforms what might be a straightforward production run into a complex web of small batches, making manufacturing flexibility an operational advantage.

- **The last stretch is where timelines quietly slip**

Final assembly and secondary packaging are often scheduled after upstream manufacturing, so delays at this stage can quickly affect the launch timeline. The physical production run is not always the primary bottleneck. Timelines are often dictated by documentation alignment, regulatory requirements and artwork approvals, which can extend timelines by three to six months and, if not integrated into the plan early, force teams into a reactive cycle.

Drug product and device components move across regions before they ever reach final assembly and packaging. Each hand-off triggers a new round of regulatory documentation and release coordination, creating an administrative lead time that can delay the entire timeline. Because these steps occur immediately before market entry, there is no buffer for error. Any administrative bottleneck directly delays patient access and halts the start of revenue.

INTEGRATED SOLUTIONS FOR GLOBAL MARKET ENTRY

To overcome these late-stage bottlenecks and successfully execute earlier global launches, sponsors require a proactive approach to their supply chain architecture. Moving away from disjointed, single-node models toward globally integrated CDMOs provides the necessary foundation for success. This approach re-

lies on three core operational solutions.

1) Redundant capacity supports recovery planning and faster regional expansion

One practical way to reduce late-stage launch risk is to treat capacity as part of business recovery planning rather than a simple scheduling problem. Redundant capacity works best when it is built on aligned execution. Operating identical assembly equipment and tooling across North America, Europe and Asia, along with consistent test methods and comparable GMP manufacturing cleanroom environments (such as Grade C and D), reduces the rework required when a program expands from one region into another. The sponsor still completes the work required for each market, but the baseline is stable enough that teams avoid rebuilding the process from the ground up.

This regional alignment supports a credible first or second source strategy. If one region faces a disruption, the sponsor can shift production to another without a full-scale revalidation. With aligned capacity available across regions, sponsors can protect continuity without requiring every change to be a full-scale revalidation project.

2) A unified quality system can reduce audit burden

A global footprint will not help much if each site behaves like a separate supplier. Fragmented quality governance stretches oversight resources and increases the audit burden. This raises the likelihood that small changes will create delays.

A unified quality and regulatory (QA/RA) framework across global sites reduces management costs and friction. Sponsors can qualify a CDMO based on a single audit or system, then manage

local differences as controlled exceptions. That approach does not eliminate market-specific requirements, but it limits how often sponsors have to repeat governance work to achieve the same outcome.

A shared framework makes timelines more predictable and reduces handoff friction, preventing quality alignment from becoming a recurring bottleneck during expansion.

3) Localized downstream operations reduce trade and tax friction

Short physical distances still introduce avoidable transaction hurdles. Shipping products across nearby borders for final assembly and then back into the target market instantly triggers multiple taxable events and documentation cycles that add cost and uncertainty.

Locating final assembly and secondary packaging in-region reduces those loops. It also shortens the feedback cycle when market requirements change because the work is closer to the teams managing artwork and release expectations. In practical terms, that localization is one of the clearer levers sponsors can use to reduce exposure to documentation delays without compromising compliance.

EXECUTING A DESIGNED OPERATING STRATEGY

While physical assets and quality frameworks are the foundation of global expansion, true manufacturing agility requires a deliberately designed operating strategy. To successfully navigate the unpredictable nature of global launches, this agility depends on having operational flexibility structurally embedded into the production model.

Although flexibility is sometimes framed as a willingness to adapt, true flex-



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ibility stems from intentional capacity design. Running standard operations on a predictable weekly cadence while protecting headroom for variability frees up capacity. For example, operating on a five-day, two-shift basis and capping baseline equipment utilization at 80% leaves nearly 40% in flexible capacity. This creates room to absorb changes through weekend time and additional shifts when delivery dates move or packaging variants change. That headroom matters most for small and mid-volume programs because these products consistently face more SKU variation and less schedule priority than the largest campaigns. The operating choices above tend to show their value most clearly in programs where timing pressure meets right-sized capacity.

CASE STUDIES IN MID-MARKET EXECUTION

The value of an agile and flexible operating strategy is most evident in the compressed launch timelines of biosimilars and the low-volume requirements of orphan drugs.

• Biosimilars

For biosimilars, operational readiness is the primary commercial differentiator. While the market opportunity is vast, the biosimilar void is widening; IQVIA reports that 90% of the 118 biologics losing exclusivity over the next decade currently have no biosimilar candidates in development.⁶

Because competition is sparse, but the patent window is short, the first mover often captures the majority of market share. In this environment, execution speed determines who wins the race to the start line. A CDMO that can skip the months of administrative setup and docu-

mentation alignment through pre-validated, redundant capacity provides a decisive advantage in capturing that first wave of revenue.

• Orphan drugs

Orphan drugs illustrate the need for high-mix agility within an underserved market. These programs face a mismatch between supply and demand: they require the same high regulatory standards as blockbusters but only produce around 30,000 units per year.

Most large-scale manufacturers prioritize equipment uptime and enforce prohibitive minimum runs, making these niche treatments commercially unviable to produce in a traditional environment. To reach vulnerable patient populations, sponsors need a partner that treats small, 5,000-unit batches – spread across the calendar – as standard operations rather than disruptive interruptions. By designing quality governance and release protocols specifically for frequent changeovers, a flexible CDMO removes the operational barrier to patient access.

THE FUTURE OF GLOBAL LAUNCH READINESS

As the patent cliff approaches in 2030, the traditional, siloed approach to drug launches is becoming an unsustainable risk. As a result, the next decade of biopharmaceutical success will be defined by the precision of the downstream supply chain.

For sponsors in the underserved middle market, survival requires shifting from reactive logistics to intentional network design. The shift toward globally integrated CDMOs is a strategic necessity to reclaim the commercial time lost during

development.

By prioritizing redundant capacity, unified quality frameworks and localized assembly, sponsors ensure they are not just ready for launch but also resilient against the inevitable disruptions of a global market. The window to recoup billions in R&D is shrinking, meaning the speed and reliability of the final mile will be the decider of patient access and commercial longevity. ♦

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BIOGRAPHIES



John Ward is Ensera's VP Pharma for the EMEA region. John is responsible for looking after pharma customers with projects in our manufacturing site

in Poland. John has been with the business for over 25 years, including setting up and running the manufacturing site in Malaysia.



Paul Hamill is Ensera's Business Development Manager for pharma services. With over 10 years of sales experience in the pharmaceutical and technical industries, Paul is responsible for working with and onboarding new customers for our site in Poland.



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- Most Advanced Phase: pre clinical
- Most Advanced Phase: phase 1
- Most Advanced Phase: phase 2
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- Multispecific Antibody: bispecific

Chart View

Table View Save Search/Create Alert Switch Search To

Company Indication Molecule/API Name Phase Most Advanced Phase Mechanism Route DD Category Tissue Targeting Dosage Form Molecule/API Type

Colorize Charts

Products & Pipeline Count vs. Most Advanced Phase

Most Advanced Phase	Products & Pipeline Count
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pre-clinical	~100
phase 1	~50
phase 2	~10
phase 3	~10

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DELIVERY SYSTEM DEVELOPMENT

Supporting Earlier Delivery-System Decisions in Injectable Drug Development Through a USP <382>-Aligned System-Level Approach

By: Sara Masucci and Crystal Salvans

INTRODUCTION

Injectable therapy development is increasingly shaped by the need for patient-centric delivery, reduced administration burden, and flexibility across clinical and commercial programs. As biologics and sensitive vaccine formulations become more complex, the packaging and delivery system play an important role in protecting product quality throughout the product lifecycle. In prefilled syringe (PFS) applications, the glass syringe, elastomeric plunger, rigid needle shield (RNS), and related interfaces must work together as an integrated container closure system.

This system-level perspective is aligned with USP <382>, Elastomeric Component Functional Suitability in Parenteral Product Packaging/Delivery Systems, which addresses functional suitability of parenteral packaging and delivery systems that include elastomeric components. Rather than focusing only on individual component properties, USP <382> supports evaluation of how component interfaces contribute to functional performance, container closure integrity, and intended use.

To support this evolving approach, the Aptar Pharma Injectables division and Stevanato Group developed a pre-evaluated package aligned with USP <382> for PFS configurations, combining glass syringes, elastomeric plungers and RNS as an assembled container closure system.

The objective is to assess how the assembled system performs and provide data that pharmaceutical developers can use during early-stage feasibility, component screening, and risk assessment activities.

A dedicated technical Data Package supports the summarized findings presented in this article and is available at both Aptar Pharma and Stevanato Group. This article provides a high-level overview of the pre-evaluated package, with the Data Package serving as the detailed evidence base for technical review.

FIGURE 1



Glass syringes from Stevanato Group (EZ-fill® Nexa® and Alba® platforms). Plungers including PremiumCoat® options and RNS for autoinjectors from Aptar Pharma.

TABLE 1	
Components Role in System Integrity	
Component	Role in System Integrity
Glass syringe barrel	Provides the primary containment structure and internal surface interfacing with the fill medium; defines the dimensional environment for the elastomeric plunger seal and contributes to overall container closure integrity.
Elastomeric plunger	Establishes the primary dynamic seal within the syringe barrel, supporting maintenance of container closure integrity during storage and simulated use while enabling controlled dose delivery.
RNS	Provides closure at the syringe tip, protecting the needle and contributing to system level container closure integrity by maintaining a sealed barrier.

A COLLABORATIVE SYSTEM-LEVEL APPROACH BUILT AROUND PRACTICAL DEVELOPMENT QUESTIONS

System Overview

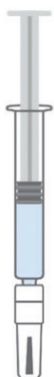
The evaluated container closure system represents a PFS primary container configuration consisting of the elements in Table 1 and Figure 1. These components are assembled to evaluate functional performance and container closure integrity independently of any specific drug product.

To evaluate component interactions

without making claims for a specific drug product or commercial lifecycle conditions, testing was performed with a placebo medium. This enabled the assessment of critical functional interactions and integrity-related behavior at system level, as a first step in the evaluation of USP <382> principles. The studies compiled in the data package characterize the baseline functional and integrity performance of the evaluated configurations detailed in Table 2 and provide early-phase, non-product-specific information to support development and de-risking activities.

The evaluated configurations are based on commercially available syringe, plunger, and RNS platforms already used in pharmaceutical development and commercial applications, including both 1mL long and 2.25mL syringe formats, allowing assessment across multiple system configurations within a common pre-verified package approach.

Because the final drug product, formulation, and processing conditions were not known at this stage, Water for Injection (WFI) was used as a neutral medium. The testing program includes:

TABLE 2						
Aptar – Stevanato Group Configurations Tested in the Data Package						
		Syringe size	1 mL		2.25 mL	
		Syringe size	Nexa®	Alba®	Nexa®	Alba®
		Needle size	Gauge: 27G and 29G, Thin Wall Length: ½"	Gauge: 27G,Special Thin Wall* Length: ½"	Gauge: 25G and 27G, Special Thin Wall Length: ½" & 8mm	Gauge: 25G and 27G, Special Thin Wall Length: ½" & 8mm
	Plunger	Coated	1mL long PremiumCoat® RTU		1-3mL PremiumCoat® RTU	
		Uncoated	1mL long RTU		1-3mL RTU	
		For Auto-Injector	½" 4900GS		1/2" & 8mm 4900GS	
	RNS	Standard	½" 4800GS		½" 4800GS	

*Stevanato Group’s Special Thin-Wall (sTW) needles feature an enlarged internal diameter to optimize the delivery of highly viscous drug formulations without the need for larger needle gauge.
The component references listed above correspond to representative platforms evaluated as part of this data package. Evaluation focused on functional interactions and system level integrity performance; no proprietary design dimensions or tolerances are disclosed.

- 1. Pull-Off Force (PoF)
- 2. Break-loose and Extrusion Force (BLEF)
- 3. Container Closure Integrity Testing (CCIT)
- 4. Seal Integrity

1. Pull-off Force (PoF)

In staked-needle PFS, the RNS must protect the needle, support closure of the syringe tip during storage, transportation and handling, and remain removable in a controlled, predictable way. This is especially important for self-administration or autoinjector integration. Pull-off force is a critical functional attribute for PFS systems equipped with RNS, reflecting the force required to remove the RNS prior to injection. If the pull-off force is too high, the user or device may struggle to remove the RNS; if too low, retention during handling, transport, or device assembly may be affected.

Test method

Aptar Pharma RNS were assembled onto Stevanato Group PFS and sterilized using Ethylene oxide (EtO). The pull-off

force was measured using a dynamometer in which the syringe was fixed while an axial displacement was applied to the RNS at a constant speed of 500 mm/min (Figure 2A). Force is continuously recorded, and the maximum value is reported as the PoF. The method is performed according to an internally validated procedure aligned with USP <382>, Section 7 (Tip Cap and Needle Shield Functional Suitability Tests), Procedure A.

Results

Within the evaluated configurations, pull-off force testing demonstrated consistent performance across EZ-fill® syringe platforms with Aptar Pharma RNS 4800GS. The graph (Figure 2B) presents one representative example from the broader testing program and illustrates observed system-level performance trends. Pull-off force values are reported as normalized values relative to the median of the tested population (median = 1.0).

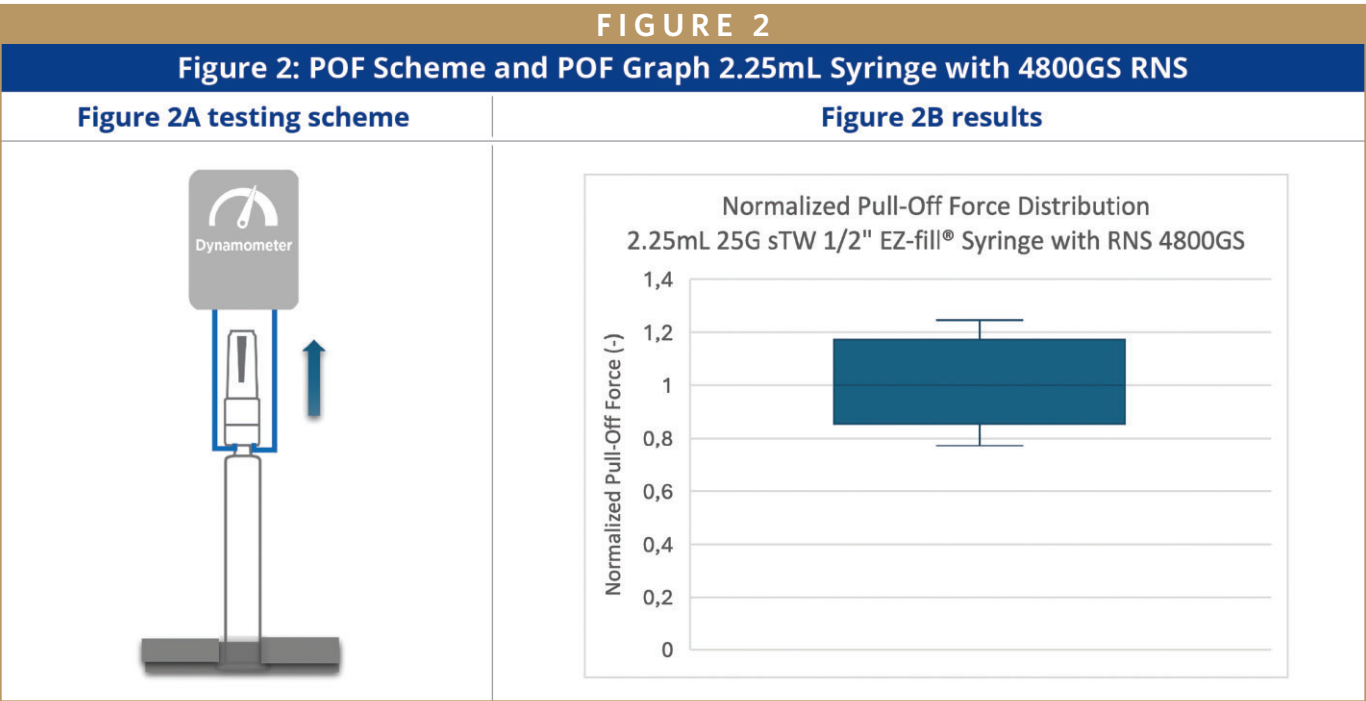
The results indicate robust compatibility between the tested Stevanato Group syringe platforms and Aptar Pharma RNS

configurations, supporting reliable shield retention without introducing excessive removal forces. Because pull-off force reflects the combined interaction between syringe, needle and RNS system-level testing provides a more realistic indication of functionality under intended-use conditions than isolated component testing separately.

2. Break-Loose and Extrusion Force (BLEF)

In PFS, the plunger must close the barrel and protect the drug during storage, transportation and handling, while delivered the dose upon activation. Break-loose force represents the force required to initiate plunger movement, while extrusion force reflects the force needed to maintain plunger travel during injection. Together, these parameters influence both functionality of the delivery system and user experience.

Aptar Pharma offers a broad range of plungers designed for compatibility with syringes and devices using ultrapure formulations. For sensitive drug products, PremiumCoat® plungers combine a fluo-



ropolymer (ETFE) film coating applied at the drug-contact surface with Aptar Pharma's 6720GS formulation and manufacturing process.

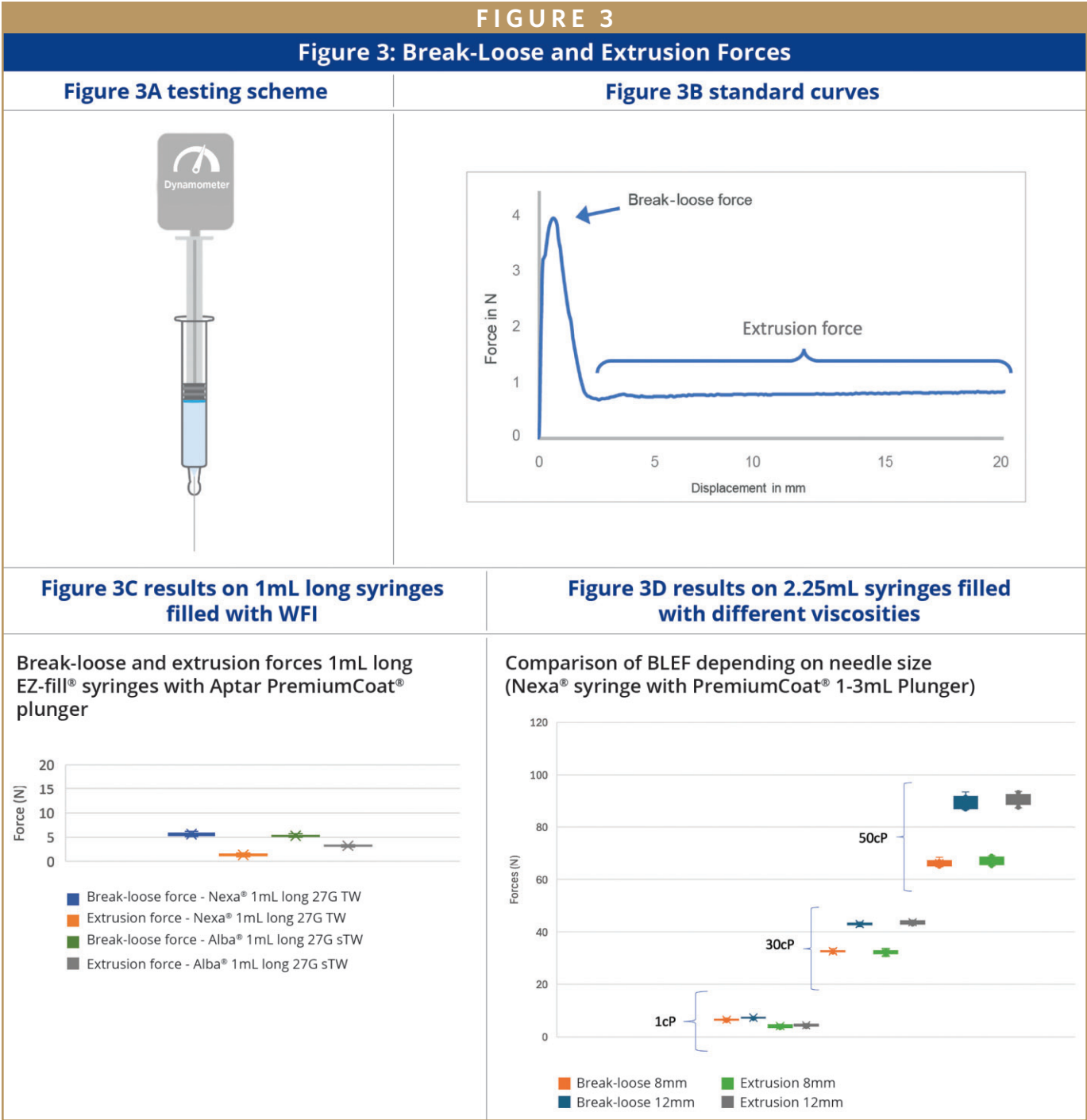
For this evaluation, Stevanato Group's Nexa® and Alba® PFS platforms were considered. In combination with these syringe platforms, Aptar Pharma's PremiumCoat® plunger was selected as a representative solution for biologic applications due to its

ETFE barrier film, designed to help minimize direct drug-elastomer interactions and support reduced extractables profiles.

Representative examples from the broader testing program included coated and uncoated plunger variants to assess break-loose and extrusion force performance across system configurations.

Test method

Break-loose and extrusion force performance was evaluated on fully assembled syringes filled with Water for Injection (WFI) as medium. Syringes were mounted in a dynamometer while controlled axial displacement was applied to the plunger at 240 mm/min, as defined by the USP <382> (Figure 3A). Force was continuously monitored throughout medium ex-



trusion to determine break-loose force, average extrusion force, and potential stick-slip behavior (Figure 3B).

The method was executed using an internally validated procedure aligned with USP <382>, Section 6.1, Plunger break-loose and extrusion force performance.

Results

Figure 3C provide representative break-loose and extrusion force performance results for selected 1mL long configurations with Aptar Pharma PremiumCoat® plungers.

When used with Alba® and Nexa® syringes, the PremiumCoat® 1mL plunger demonstrated improved consistency and reduced variability. These results are supported by the interaction between the syringe barrel surface and the proprietary three-rib plunger design, which maintains continuous contact with the barrel and supports smooth force profiles during injection.

As injectable therapies become more concentrated and potentially more viscous, actuation performance becomes increasingly important. Break-loose and extrusion force performance can significantly affect usability (Figure 3D). The speed was set at 300mm/min. The 8mm needle demonstrated a mechanical advantage over the 12.7mm configuration across the viscosities tested. At 50 cP, injection forces were reduced by approximately 25%, supporting the suitability of the 8mm needle for higher-viscosity drug products. While these measurements represent mechanical performance characteristics rather than clinical outcomes, they illustrate how system-level evaluation can identify configurations that support functionality and usability objectives in combination products.

3. Container Closure Integrity Testing (CCIT)

Container closure integrity remains a critical requirement for injectable packaging systems. A delivery system must maintain sterility and protect product quality throughout its lifecycle while remaining capable of delivering the drug safely and effectively. As regulatory expectations and industry focus continue to shift toward deterministic container closure integrity testing (CCIT), helium leak detection has emerged as a powerful analytical tool for investigating packaging system integrity.

Test method

Container closure integrity was evaluated using helium mass spectrometry operated in accumulation mode. Test samples were exposed to helium tracer gas, and helium transmission through potential leak pathways was measured using a calibrated high-sensitivity detector (Figure 4A). This approach enabled assessment of sealing performance at glass-elastomeric component interfaces or assembled-system levels, providing quantitative information on integrity performance across the evaluated configurations. Testing followed deterministic tracer-gas leak detection principles described in USP <382> Packaging/Delivery System Integrity Tests, with reference to USP <1207>, and was performed using an internally validated procedure.

Results

The results (Figure 4C) remained substantially below the reference limit reported within the study framework from the USP <382> guideline, supporting the assessment of container closure integrity performance for the evaluated configurations.

4. Seal Integrity

As injectable drug products become more complex and delivery systems evolve toward patient-centric designs, maintaining functional seal integrity during administration is increasingly important. USP <382> introduced dedicated functionality tests to evaluate the ability of elastomeric closure components to maintain sealing performance under conditions representative of use. Through the collaboration between Aptar Pharma and Stevanato Group, coated and uncoated plunger technologies were assessed within Nexa® and Alba® prefillable syringe platforms under challenging functional conditions. This system-level evaluation supports a broader understanding of dynamic seal integrity across representative component combinations.

Test method

Syringe systems were filled with a fluorescent tracer solution and challenged under controlled pressure conditions designed to simulate stresses experienced during drug administration. An axial force corresponding to an internal pressure of 300 kPa was applied and maintained for 30 seconds at a crosshead speed of 20 mm/min (Figure 4B). Following testing, samples were inspected under UV light for evidence of tracer migration across critical sealing interfaces. The absence of fluorescence outside the sealing area was considered evidence of maintained seal integrity. The method was executed using an internally validated procedure aligned with USP <382>, Section 6.2 (Plunger Seal Integrity), Procedure A.

Results

For all evaluated configurations, including coated and non-coated plunger variants, no infiltration events were ob-

served. All tested samples achieved 0/10 infiltration results.

Although plunger seal integrity testing is a pass/fail assessment, the results provide additional confidence in sealing performance and consistency across the evaluated component combinations.

CONCLUSION

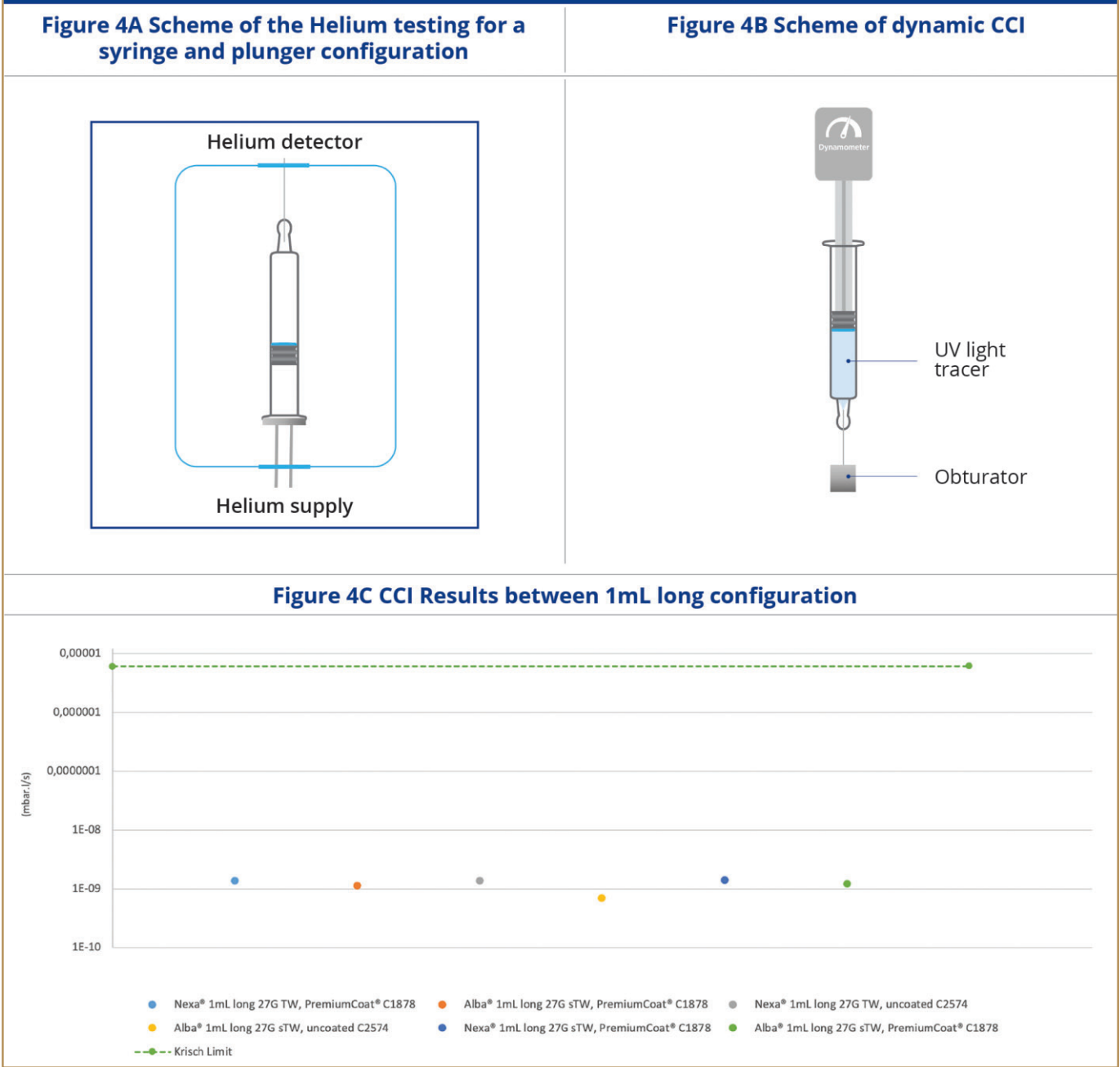
USP <382> represents an important evolution in the evaluation of injectable packaging and delivery systems. By focusing on functional suitability at system level, it reflects combination product development realities, where performance depends on the interaction of multiple

integrated components.

The collaborative study conducted by Stevanato Group and Aptar Pharma illustrates how USP <382> principles can be applied in practice. Across the evaluations, the combined prefillable syringe, plunger, and RNS generated consistent system-level performance data across the evaluated configurations.

FIGURE 4

Figure 4: Container Closure Integrity



The findings highlight the value of generating system-level data early in development to support more informed packaging decisions as formulation complexity continues to increase.

For further details, contact Aptar Pharma or Stevanato Group to access the data package summarizing the system evaluation findings. ♦

To view this issue and all back issues online, please visit www.drug-dev.com.

BIOGRAPHIES



Sara Masucci is Product Manager at Stevanato Group, focusing on syringe container solutions. Sara holds a Master's degree in Business Administration from the University of Padua. She has over three years of experience in the pharmaceutical packaging and medical device industry, having built expertise in both Product Development and Product Management.



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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LYOPHILIZATION

Great Expectations: Selecting & Managing CDMO Partnerships for Lyophilized Injectables from Development Through Commercialization

By: Carrie A. Shults

INTRODUCTION

Outsourcing to Contract Development and Manufacturing Organizations (CDMOs) has become a common practice across pharmaceutical and biotechnology companies as pipelines expand, timelines compress, and internal resources remain constrained. Selecting the right partner directly influences development speed, program cost, technical risk, and the likelihood of a successful transition from development to clinical manufacturing.

For lyophilized sterile injectables, the stakes are even higher. Freeze-dried products present unique formulation, processing, analytical, and manufacturing challenges that require specialized expertise. This guide outlines practical considerations for selecting and managing CDMO partnerships from early development through clinical trial material (CTM) manufacturing and beyond, with an emphasis on technical capability, governance, and risk management rather than marketing claims.

STRATEGIC VS. TACTICAL PARTNERSHIPS: CHOOSING THE RIGHT MODEL

Organizations typically engage CDMOs using one of two approaches. A strategic partnership involves a long-term relationship in which a single provider supports multiple functions across development and manufacturing. This model works well when portfolio continuity, knowledge retention, and integrated execution are priorities.

A tactical partnership focuses on a defined scope of work, such as formulation development, lyophilization process design,

analytical testing, or clinical manufacturing. This approach can provide access to highly specialized expertise without committing an entire program to a single provider.

Neither model is inherently superior. The appropriate choice depends on program objectives, available internal expertise, risk tolerance, and development timelines. Many organizations successfully combine both approaches by maintaining strategic relationships for core activities while engaging technical specialists for specific challenges.

MAPPING THE CRITICAL PATH

The major development milestones for most injectable products are similar, but lyophilized products require greater attention to interactions among activities that are often managed independently. Critical development areas include:

- API and/or DS manufacturing and characterization
- Analytical method development and qualification
- Product design and presentation selection
- Formulation development
- Lyophilization feasibility and process development
- Aseptic process engineering
- Clinical manufacturing and technology transfer planning

Few organizations excel equally across all disciplines. Effective project management depends on assembling the right expertise at the right time while ensuring decisions in one area support downstream manufacturing and regulatory objectives. Importantly, development activities should never be viewed in iso-

lation. Early formulation and process development decisions can significantly influence manufacturing success, scalability, product robustness, and future technology transfer efforts.

WHY LYOPHILIZATION REQUIRES SPECIALIZED EXPERTISE

Lyophilized injectables present unique technical considerations that should influence both development strategy and partner selection.

Sterility & Aseptic Operations:

Lyophilized drug products are typically sterile injections. Successful programs require integration of aseptic processing principles with lyophilization process development from the earliest stages.

Container-Closure Considerations:

Vial geometry, stopper design, venting characteristics, and seal integrity can affect moisture content, reconstitution time, sterility assurance, and long-term stability.

Critical Quality Attributes (CQAs):

Residual moisture, reconstitution time, potency retention, and particulate burden are especially sensitive to formulation and processing conditions.

Regulatory Complexity:

Although global harmonization efforts continue, many regulatory expectations were initially developed around liquid products. Consequently, lyophilized products often require greater scientific justification and documented rationale throughout development.

Many organizations own lyophilization equipment; far fewer possess the scientific foundation and process engineering and manufacturing expertise required to consistently design robust processes which scale and transfer successfully between facilities. As outsourced options continue to expand, sponsors should evaluate demonstrated technical experience and performance rather than relying solely on equipment lists or facility size.

It is also important to recognize that many CDMOs transfer products and processes from a development laboratory to a clinical manufacturing setting, and ultimately to commercial scale manufacturing facility. In some cases, this may be different buildings on a single site, or entirely different sites, and even different countries.

WHAT GOOD LOOKS LIKE IN A LYOPHILIZATION CDMO

When evaluating potential partners, focus on evidence of technical capability and operational execution.

Flexibility with Control:

Phase I and Phase II programs often operate under evolving timelines, limited API or Drug Substance availability, and changing clinical requirements. Strong CDMOs adapt development plans, batch sizes, and study designs while maintaining GMP compliance, data integrity, and disciplined change management. They openly discuss development tradeoffs rather than forcing programs into predefined service packages.

Scientific Depth Beyond Equipment:

Technical expertise should extend well beyond access to manufacturing assets. Effective providers begin with the Target Product Profile (TPP) and consider route of administration, formulation constraints, stability requirements, and future commercial goals when developing product and process strategies. Similar to transferring a process from development into a manufacturing operation, the success of transferring the early TPP to Critical Quality Attributes (CQA is dependent on a level of experience and expertise.

Sponsors should seek evidence that formulation development, process engineering, analytical development, and manufacturing activities are aligned within a common development framework. This integration helps avoid costly redesigns later in development and improves technology transfer success.

Integrated Capabilities:

Sponsors do not necessarily need a provider that performs every function internally. However, they should ensure the CDMO can effectively support the activities most critical to program success based upon their strengths and expertise. For lyophilized products, those capabilities typically include:

- Formulation development
- Product characterization
- Lyophilization process design
- Sterile product clinical manufacturing
- Technology transfer planning
- Analytical support

Cross-functional collaboration among scientists, engineers, quality professionals, and manufacturing personnel is often a stronger predictor of success than the breadth of a provider's service portfolio.

Communication & Governance:

Technical expertise alone cannot overcome poor project execution. Successful partnerships establish routine communication, clearly defined responsibilities, structured decision-making processes, and proactive change management. Regular working meetings and periodic strategic reviews help teams address issues before they become critical delays.

A PRACTICAL APPROACH TO CDMO SELECTION AND ONBOARDING

Step 1: Translate the TPP into Scientific & Technical Requirements

Define the product needs such as intended use, dosage form, presentation, storage requirements, shelf-life expectations, and reconstitution requirements. These elements should drive development strategy and CDMO selection.

Step 2: Build an Evidence-Based RFP

Avoid generic capability and commercial aspect checklists. Instead, ask potential partners to describe their development philosophy, approach to process design, quality systems, and technology transfer practices. Request examples of how they assess risk, manage limited API or Drug Substance supplies, establish development priorities, and make critical decisions. The goal is to evaluate scientific rigor, problem-solving capability, and operational maturity without requiring disclosure of confidential client programs.

Step 3: Evaluate API-Constrained Development Strategies

Many early-stage programs operate with limited API or Drug Substance sup-

plies. Assess how prospective partners conserve material during formulation studies, process development, engineering runs, and GMP manufacturing. Small-scale modeling approaches can be valuable when supported by sound scientific justification.

Step 4: Review Quality Systems Through a Lyophilization Lens

Standard GMP assessments remain essential, but sponsors should also evaluate how quality systems address lyophilization-specific risks. This encompasses a level of control to achieve process reproducibility, product consistency, and batch uniformity.

Examples include:

- Complete sublimation without collapse or melt-back
- Moisture variability
- Visual cake defects
- Vial-to-vial variability

A strong quality organization understands how these risks relate to both process performance and patient safety.

Step 5: Confirm Analytical Readiness

Analytical methods frequently become hidden critical activities. Ensure methods adequately support product characterization, stability assessments, release testing, and process understanding. Assays should be phase-appropriate while remaining capable of supporting future development needs.

When testing is outsourced, confirm the CDMO has established relationships with qualified laboratories and robust procedures for sample management, method transfer, and data review.

Step 6: Establish Governance Early

Define escalation pathways, decision rights, communication expectations, and change control processes before project execution begins.

Strong governance helps teams respond quickly when technical or operational issues arise.

DESIGNING FOR SCALE & TECHNOLOGY TRANSFER FROM DAY ONE

One of the most common and costly mistakes in lyophilized product development is treating transferability as a later-stage activity. In practice, many manufacturing challenges can be traced back to early development decisions that inadvertently limited process robustness or scalability. The goal in developing a product and engineering a process to be safe, effective, and sufficiently robust is an essential focus in even early planning. The most effective partners build transferability into development activities from the outset.

Build Process Robustness:

Avoid processes that operate at the edge of acceptable performance. Design processes with sufficient operating ranges to accommodate normal variability among facilities, equipment, and material lots.

Make Scalable Component Decisions:

Container-closure systems selected during development should be commercially available and scalable to larger manufacturing volumes. Potential differences in stopper performance, vial geometry, or component sourcing should be assessed early. Recognize that the primary

packaging has a significant influence on product quality outcomes.

Standardized Data Collection:

Consistent collection of Critical Process Parameters (CPP) of shelf temperature, chamber pressure and time, and key resulting parameters of product temperature and process performance data improves comparability across development, clinical manufacturing, and eventual commercial operations.

When transferability becomes a development objective rather than an afterthought, technology transfer becomes substantially less complex and less risky.

CLINICAL TRIAL MATERIAL PLANNING & RISK MANAGEMENT

Early clinical manufacturing programs must balance speed, learning, flexibility, quality, and cost. A practical approach begins with scheduling activities based on clinical timelines and API or Drug Substance availability. Programs should be back-planned from key milestones such as first-patient-in dates, enrollment schedules, distribution channels, and stability requirements.

Risk management is equally important:

Technical Risks: Common lyophilization risks include:

- Product collapse
- Melt-back
- Excess residual moisture
- Slow reconstitution
- Product heterogeneity
- Moisture-driven degradation

Mitigation strategies may include feasibility studies, design-of-experiments (DoE) approaches, process characterization, establishing a Proven acceptable range (PAR), and clearly defined acceptance criteria.

Operational Risks:

Potential operational challenges include:

- Process excursions
- Equipment downtime
- Material shortages
- Scheduling conflicts
- Resource constraints

Integrated project schedules, contingency planning, and secondary suppliers for critical materials can help reduce risk exposure.

Regulatory Risks:

Development programs should maintain clear scientific justifications for formulation and process decisions, particularly when existing regulatory guidance does not directly address product-specific circumstances. Contemporaneous documentation is essential from the outset. It simplifies future submissions and supports comparability assessments when development changes occur.

COLLABORATION PRACTICES THAT KEEP PROGRAMS MOVING

The mechanics of collaboration often determine how efficiently technical challenges are resolved. Successful partnerships are characterized by:

- Transparency regarding risks and challenges
- Clearly defined responsibilities

- Formal change management processes
- Routine communication
- Shared commitment to problem solving

Weekly working sessions combined with periodic strategic reviews help maintain alignment while allowing teams to quickly address emerging technical, operational, and regulatory issues.

COMMON PITFALLS AND HOW TO AVOID THEM

Confusing Equipment with Expertise:

Owning a lyophilizer does not guarantee competence in formulation science, process development, aseptic manufacturing, or technology transfer. Success of Lyophilization depends on scientific depth, process understanding, and execution discipline, not simply the presence of hardware.

Evaluate experience, scientific capabilities, and demonstrated outcomes in addition to equipment inventories.

Designing Processes Without Transferability:

Development processes optimized exclusively for a specific laboratory system may become difficult to reproduce elsewhere. Build robustness and transfer considerations into process design from the beginning.

Delaying Container-Closure Decisions:

Vials and stoppers can influence residual moisture, product appearance, process performance, and reconstitution behavior. Establish and verify container-closure strategies as early as practical.

Overlooking Governance:

Unclear responsibilities and poorly defined decision-making processes can slow even technically successful programs. Governance expectations should be documented in project agreements and operational plans before work begins.

BRINGING IT ALL TOGETHER

For lyophilized sterile injectables, successful progression from development through clinical manufacturing depends on selecting partners with the right combination of scientific expertise, manufacturing capability, and project leadership.

While flexibility, quality systems, and communication remain essential, the strongest predictor of long-term success is often a partner's ability to translate development knowledge into scalable, transferable manufacturing processes. Sponsors should prioritize organizations that integrate formulation science, process engineering, analytical strategy, and manufacturing execution within a cohesive technical framework.

Organizations that emphasize technical depth, proactive risk management, and development-to-manufacturing continuity are better positioned to reduce timelines, control costs, and generate reliable clinical trial materials that support future commercialization.

By selecting the partnership model that best aligns with program objectives, insisting on demonstrated lyophilization expertise, and maintaining disciplined governance throughout execution, sponsors can improve the probability of delivering high-quality clinical materials on time and with confidence in the path forward. ♦

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BIOGRAPHY

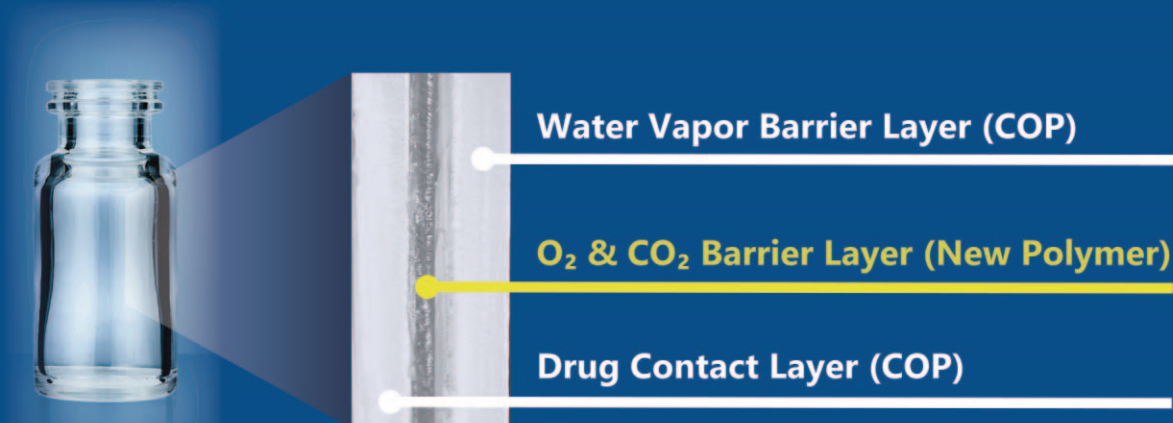


Carrie A. Shults is Director of Operations at LTI, providing strategic leadership across manufacturing, development, and maintenance functions. With more than 25 years of experience in academia and the pharmaceutical industry, she previously held roles at Merck and GlaxoSmithKline. Carrie holds BS and MS degrees from Neumann and Drexel Universities, has published extensively, and is active in AAPS, ACS, ISL-FD, and PDA.

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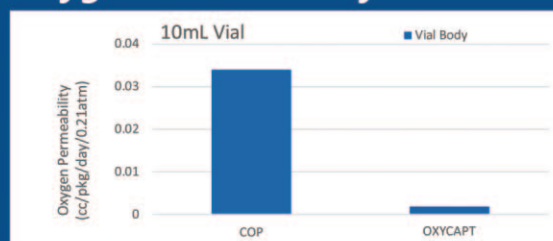
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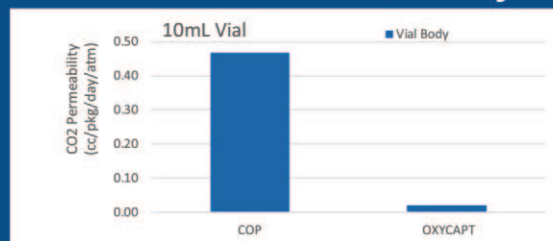


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SPECIAL FEATURE

Injection Devices: Advancements Converge to Expand Patient Possibilities

By: Cindy H. Dubin, Managing Editor

Innovation. That is the answer device manufacturers give when asked what excites them most about today's injection devices. From needle-free injections to more intuitive design, device developers aim to maximize patient adherence. One example of designing for adherence comes from LG Chem, which presented long-term safety and efficacy data in May for its Eutropin growth hormone therapies, and also introduced the EcoPen injection device. So Jin-eon, Head of LG Chem's Research and Development Division, said EcoPen was developed based on the company's "3-Comfortable" framework, which was derived from analyses of treatment experiences reported by patients, caregivers, and healthcare professionals. "Beyond improving the device itself, we focused on reducing the psychological and physical burden experienced by children and caregivers during injections," So said. "We expect



PremiumFill® components produced under enhanced cleanroom controls (Aptar Pharma).

EcoPen to improve treatment adherence in real-world settings.”

Device developers are focused on the home setting, in particular. Perhaps no treatment has driven self-administration faster than the GLP-1 sector. For example, earlier this year, Eli Lilly unveiled a month-long injectable device for Zepbound designed to make the treatment more convenient. Instead of using a single-dose autoinjector each week, patients can store a month’s worth of medication in one pen, reducing the number of devices patients must manage and simplifying the treatment routine. Previously, most Zepbound users relied on weekly, single-dose autoinjector pens. Others used single-dose vials that require drawing the medication into a syringe before self-injection. The multi-dose device – called the KwikPen – streamlines that process, eliminating repeated packaging and preparation.¹

Stevanato Group’s multi-device for GLP-1 delivery addresses the shift towards patient-centric models of care and self-administration. The company just received European marketing authorization for its liraglutide-based combination products incorporating Stevanato Group’s proprietary Alina® pen injector platform. The approved configurations include Alina 30, developed for liraglutide-based therapies for diabetes, and Alina 50, designed for liraglutide-based weight management applications. Both variants are part of Stevanato Group’s broader Alina variable-dose pen injector platform, which offers multiple pre-configured variants for GLP-1s and other injectable therapies. Alina features a dial-a-dose mechanism with visual, audible, and tactile feedback during dose selection and injection, and compatibility with ISO

standard 3mL glass cartridges. The platform has been designed to support manufacturing scalability, and integration into existing pharmaceutical fill and finish and final assembly supply chains.

At-home subcutaneous (SC) self-administration marks a significant transition from intravenous (IV) hospital settings, particularly for delivering more complex biologic therapies and larger volumes. In July, Eisai Co., Ltd. and Biogen Inc. announced the FDA approval of a supplemental Biologics License Application (sBLA) for a once-weekly lecanemab-irmb subcutaneous injection as an initiation dose for the treatment of early Alzheimer’s disease. LEQEMBI is administered via the LEQEMBI IQLIK autoinjector, an SC alternative to IV dosing from the start of treatment.

Similarly, the FDA recently approved Sanofi’s SC Sarclisa (isatuximab-irfc) Escena in combination with standard-of-care regimens for the treatment of patients with multiple myeloma (MM) across all existing indications of Sarclisa IV formulation. With the approval, Sarclisa Escena is the first anticancer treatment to be administered through both an on-body injector (OBI; via the CirCLIQ®) and manual SC administration. The OBI uses a retractable 30g needle that is shorter and thinner compared to the needles commonly used for large-volume injections. The approval of Sarclisa Escena with Enable Injections’ CirCLIQ OBI – developed using the enFuse® platform

“What excites me most is the opportunity to fundamentally change where and how advanced therapies are delivered,” says Patrick Anquetil, PhD, Chief Executive Officer, Portal Instruments. “Over the past several decades, the

biopharmaceutical industry has made extraordinary progress in discovering increasingly powerful biologic medicines. The next frontier is ensuring those therapies can be delivered conveniently, reliably, and comfortably to patients. As biologics become larger, more complex, and more personalized, delivery technology will increasingly determine whether a therapy requires an infusion center visit or can be administered at home.”

As delivery platforms reach a broader range of patients in their preferred settings, access to therapy becomes virtually unlimited, say industry insiders. These devices are becoming more intuitive, scalable, and smarter. Consider Remedy Place has launched the NAD+ Smart Pen, a next-generation injectable designed to make clinical-grade NAD+ accessible at home. Developed in exclusive partnership with UK-based NADclinic, the pen contains 1,000 milligrams of high-purity NAD+, a naturally occurring coenzyme involved in cellular energy metabolism. The NAD+ Smart Pen contains no stabilizers, fillers, or synthetic additives, preserving the integrity of the molecule. According to a press statement, Remedy Place is calling the NAD+ Smart Pen “the most advanced smart pen delivery system available, elevating precision, accessibility, and performance in one seamless solution.”

Another smart injection technology comes from a partnership between Aptar Digital Health and Enable Injections, Inc. Aptar Digital Health is now Enable’s preferred digital health partner for the enFuse® On-Body Delivery System. This digital solution is designed to guide patients and caregivers throughout the injection process and support patient

adherence. According to a press release, adherence data and patient reported outcomes will be captured remotely, securely stored and made available through analytics dashboards that generate actionable insights intended to support clinical development, launch readiness and real-world use.

"I believe we are entering an era where intelligent delivery systems will become as important as the drug itself," says Anquetil. "The convergence of biologics, digital health, connectivity, and closed-loop-controlled delivery has the potential to improve adherence, generate valuable treatment insights, and bring therapies once confined to hospitals and infusion centers directly to patients. Ultimately, success will be measured not by what the device can do, but by what it enables."

Katie Falcone, Director, Technical Services, Integrated Systems, West, adds: "I am particularly encouraged by how these innovations are coming together with a stronger focus on the patient. As we continue to learn more about usability and real-world use, we can design delivery systems that not only meet technical requirements but also fit more seamlessly into patients' lives. Overall, I see a future where we can take increasingly complex, lifesaving therapies and deliver them in ways that are more optimized, more accessible, and ultimately more supportive of patient independence."

This exclusive annual *Drug Development & Delivery* report highlights some of the most innovative and patient-centric injection device platforms, the needs they fulfill in the market, and how they make treatments more accessible.

Aptar Pharma: Reducing Scrap Rates by Over 20% with Advanced Injectables Closure Systems

Particulate contamination remains one of the leading causes of injectable drug product recalls. A single defect can lead to the rejection of an entire finished batch. With EU GMP Annex 1 setting stricter expectations on contamination control, closure quality has become a key factor in fill-finish efficiency and total cost of ownership for pharmaceutical manufacturers.

"Primary packaging is often overlooked as a lever to reduce fill-finish rejections, yet closure quality directly influences batch outcomes," says Estelle Verger, Business Development Senior Manager, Aptar Pharma. "With this in mind, we designed PremiumFill® to deliver meaningful improvements on the defect categories that matter most to our customers."

Aptar Pharma's PremiumFill vial stoppers and prefilled syringe plungers are produced under enhanced specifications for fibers, embedded and foreign particles, metallic particles, and biological contamination. Molding and trimming are performed in ISO 7 cleanrooms with robotized handling; components undergo metal detection before packaging. The result is tighter defect limits on the categories most often responsible for rejection at the fill-finish stage, she says.

The operational benefit was measured in a case study run at a global biopharmaceutical manufacturer's facility. The customer switched from a standard vial stopper to an Aptar Pharma PremiumFill stopper on an infusion product and inspected finished units using automated vision, comparing lots produced with each closure.

"Over nine months of operation, the customer reported a reduction in scrap rate of over 20%, with the most significant improvements observed on fiber contamination and stains," says Ms. Verger. "The 20% scrap reduction translated into better line yield and improved fill-finish efficiency for our customer. It also confirms that closure quality can have a measurable impact on operational performance, especially when contamination control expectations continue to rise."

She adds that this case study demonstrates that stopper selection is more than a compliance or packaging decision. By reducing visible defects at the fill-finish stage, enhanced closure quality can help cut avoidable scrap, improve line yield, and create a measurable total cost of ownership benefit for injectable manufacturers.

BD Pharmaceutical Systems: Advancing Subcutaneous Delivery of High-Dose Therapies

The rise of high dose subcutaneous therapies is creating new delivery challenges, as formulations become more complex, more viscous, and larger in volume. BD addresses these challenges through patient-centric product innovation and strategic partnerships with customers and industry partners. Examples include its prefillable syringes and wearable injectors, translational research capabilities, and a strategic partnership around device integration.

The new BD Neopak™ XtraFlow™ Glass Prefillable Syringe 5.5mL leverages BD advanced technologies, including a shorter, 8-millimeter needle and thinner wall cannulas, to support the delivery of higher volume and viscosity medicines. "These enhancements should enable im-

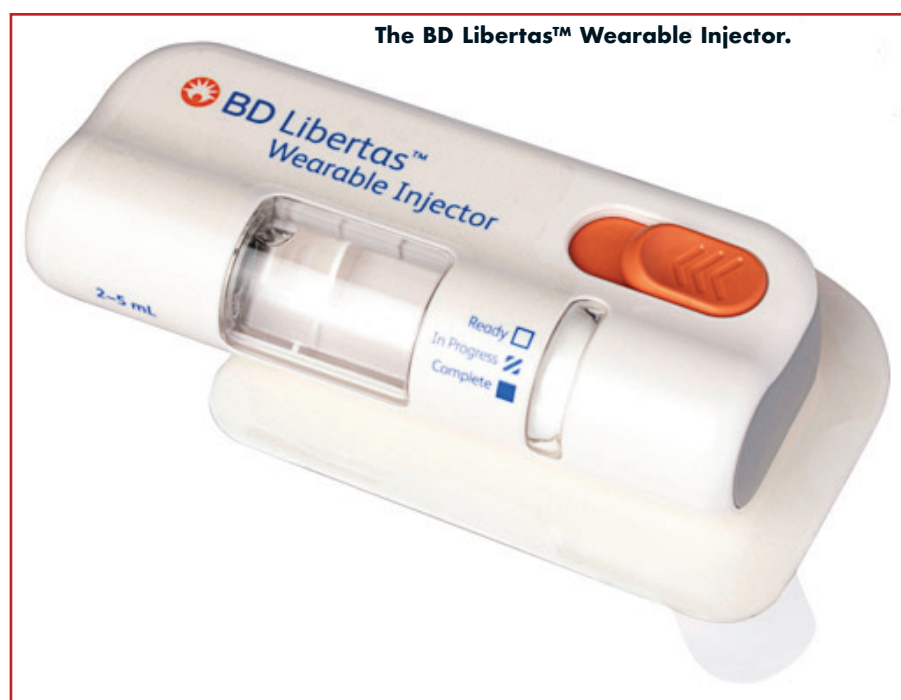
proved injection time and optimized flow, addressing common challenges with large-volume biologics and enabling drug developers to move beyond the limitations of standard syringe offerings,” says Beth DiLauri, WW Director, Global Marketing, BD Pharmaceutical Systems.

For therapies with high-dose formulations that require extended injection times, BD offers the BD Libertas™ Wearable Injector with Peel, Stick & Click™ technology. The patient ready-to-use and fully mechanical design is intended to simplify delivery of large volume and/or high-viscosity fixed-dose injections. Patients will receive the drug without having to assemble the delivery system or transfer the drug. There is no battery or electronics to complicate pharma development and validation or patient use.

“Additionally, BD’s translational research experience and body of pre-clinical injection science data has helped inform pharma and retire risk on their time to market pathway,” she says. “This expertise continues to expand with new technologies and alternatives entering the market. For example, recent research has studied the delivery of formulations with and without hyaluronidase using BD Libertas™ Wearable Injector, showing positive results.”

BD is also working with industry partners on device integration. The company is strengthening its collaboration with Ypsomed while working on the 5.5mL version of the BD Neopak XtraFlow Glass Prefillable Syringe. This is designed to be fully compatible with Ypsomed’s YpsoMate® 5.5 autoinjector platform, expanding options for pharmaceutical companies and patients who require large-volume subcutaneous self injections.

BD also partnered with a pharma company evaluating a high-dose, high-vis-



cosity biologic for subcutaneous delivery. The key question was whether an on-body delivery system could successfully support the product’s clinical and commercial objectives. A cross-functional team of subject matter experts developed and executed a targeted evidence-generation plan using the BD Libertas™ Wearable Injector.

“Through a combination of predictive modeling, bench testing, and *in vivo* studies, we generated a comprehensive understanding of product performance across a range of delivery conditions,” explains Ms. DiLauri. “The outcome was a data-driven assessment that informed our pharma partner’s objectives and decision making.”

Credence MedSystems: Balancing Sustainability, Usability & Manufacturing Efficiency

The continued growth of biologics, monoclonal antibodies and GLP-1 therapies is accelerating the transition towards larger-volume subcutaneous injections, particularly in 3mL and 5mL formats. While these therapies offer important clinical benefits through higher doses and less fre-

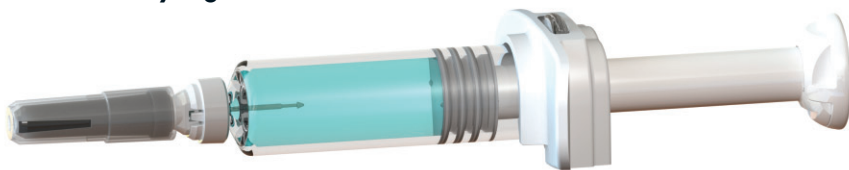
quent administration, they also present a significant challenge for device developers.

“Larger injection systems typically require more plastic, which means a bigger device footprint and, so, increased packaging. This in turn places greater demands on manufacturing, logistics and disposal,” says Sian Eden, Commercial Director, Credence MedSystems. “Our industry must continue to deliver improved patient experiences while reducing environmental impact without introducing additional complexity for pharmaceutical manufacturers.”

Credence MedSystems believes the solution lies in designing sustainability into the device from the outset, rather than adding it as an afterthought. The Credence Companion® prefilled syringe platform integrates passive needle retraction within the syringe itself, eliminating the bulky external plastic safety assemblies commonly used on conventional safety syringes.

“The result is a familiar syringe format that incorporates passive safety and intuitive audible, tactile and visual end-of-dose confirmation while reducing the additional material typically associated

The Credence Companion® enables passive, integrated needle safety and intuitive usability, and is ready-to-supply in 1mL, 2.25mL, 3mL and 5mL syringe barrels.



with larger-volume injection devices,” she says.

As the market moves towards 3mL and 5mL injectable therapies, the benefits of Companion’s integrated design become increasingly significant, adds Ms. Eden. Reducing material usage can lower packaging requirements, transportation volumes, warehouse footprint and cold-chain space, while the smaller Companion Syringe post-use profile helps reduce sharps waste. “These efficiencies demonstrate that sustainability and operational performance are not competing priorities but can be advanced together through thoughtful engineering,” she says.

Equally important is ensuring that innovation integrates seamlessly with established pharmaceutical manufacturing processes. Device platforms that are compatible with existing fill-finish operations and standard syringe formats enable manufacturers to adopt new technologies with lower implementation risk while maintaining established production efficiencies. This approach allows innovation to focus on improving patient safety and usability without disrupting proven manufacturing infrastructure.

Looking ahead, the most exciting opportunity in injectable drug delivery is the convergence of patient-centered design, sustainability and manufacturability, says Ms. Eden.

“Future injection systems must not only support increasingly complex biologic therapies but also minimize environmental

impact and integrate efficiently into pharmaceutical production,” she says. “Innovation that successfully balances these objectives will help shape the next generation of injectable drug delivery and ensure that advances in therapy are matched by advances in device design.”

Datwyler: Filling a Gap in Large-Volume Delivery

The larger volume delivery space (>10mL) continues to be a high-demand area for drug delivery systems, and as the pharmaceutical space continues to move

towards high viscosity biologics (e.g. monoclonal antibody-based therapies), the need for larger volume container closure components, such as syringe or cartridge plungers, will continue to increase. Additionally, drug compatibility with container closure components is, and will continue to be, a challenge. Extractables and leachables (E&L), silicone particles, particulates, etc., will need to be addressed to ensure drug purity and efficacy when delivered to the end user.

Datwyler’s NeoFlex™ portfolio of plungers addresses the needs of drug compatibility by delivering a low E&L profile and clean rubber elastomer that ensures drug compatibility concerns are alleviated throughout the drug delivery device development lifecycle, explains Yitian Xiao, Global Biologics Product Expert, Datwyler.

Datwyler’s 20mL V9621 NeoFlex fluoropolymer spray-coated plunger enables

Datwyler’s 20mL Coated Plunger for large-volume on-body delivery.



smooth, low variability gliding performance when integrated into a 20mL glass cartridge-based drug delivery system, he says. The low variability gliding ensures that drug delivery injection times are predictable, improving patient comfort and increasing likelihood of patient adherence to their therapies.

"As the first to market 20mL spray-coated plunger, V9621 NeoFlex has filled the gap in the large-volume delivery space, allowing pharmaceutical partners to develop a large-volume delivery device for a therapy that could only be delivered in large-volume applications," he says. "This advances therapies through clinical trials that were once not possible but have been enabled by the incorporation of this novel 20mL plunger to their chosen drug delivery system."

NeoFlex also incorporates an energy-efficient spray coating technology that has a 50% lower carbon footprint compared to traditional fluoropolymer film-coating application for plungers. In fact, in 2024 and 2025, Datwyler received the Ecovadis Platinum rating – the highest possible rating – for its sustainability efforts through many initiatives and metrics incorporated in its global processes.

Mr. Xiao says: "This portfolio of plungers balances functionality, chemical cleanliness, and sustainability to ensure a high quality product for our pharmaceutical partners in their container closure system development."

DDL, Inc.: Developing Phase-Appropriate Analytical Strategies & Testing Roadmaps

One of the most significant challenges in injectable drug delivery is navigating the evolving regulatory landscape

surrounding combination products while ensuring product performance, functionality, and integrity. As regulatory expectations, standards, and guidance documents continue to advance, pharmaceutical and biotechnology companies must demonstrate that their delivery systems consistently perform as intended throughout development, commercialization, and lifecycle management.

DDL, Inc. supports clients by helping them interpret and apply these complex regulatory and industry requirements. This is particularly important for autoinjectors, pen injectors, and other delivery systems that incorporate prefilled syringes or cartridges, where selecting the appropriate performance and functional testing methodology is critical.

"Our team works closely with customers to develop phase-appropriate analytical strategies and testing roadmaps tailored to the specific combination product," says Jennifer Riter, Vice President of Analytical Testing Services, DDL. "We provide guidance on test method development, validation, and regulatory expectations, ensuring that all necessary performance evaluations are incorporated into a comprehensive testing program."

In addition, DDL performs testing in a cGMP-compliant, FDA-registered laboratory, delivering the data needed to support product development, regulatory submissions, commercialization, and ongoing lifecycle management. By combining scientific expertise with regulatory insight, DDL helps clients navigate the complexities of combination product development while accelerating their path to market, she says.

The future of injectable drug delivery is particularly exciting because of the rapid pace of innovation focused on improving

patient outcomes, convenience, and treatment adherence. Emerging delivery technologies are enabling more efficient and effective administration of complex therapeutics while enhancing the overall patient experience.

As these systems become increasingly sophisticated, they also present new challenges for product evaluation and verification. Novel device designs often require the development of equally innovative testing methodologies to adequately assess performance, functionality, usability, and product integrity. Relevant examples include luer activated valves (LAVs) under ANSI/AAMI CN27 and novel container closure systems evaluated under USP 1207.

"At DDL, we are energized by the opportunity to support these advancements," says Ms. Riter. "As injectable delivery technologies continue to evolve, we remain committed to developing cutting-edge test methods and analytical approaches that help bring innovative therapies to patients safely, effectively, and with confidence. The continued advancement of both drug delivery systems and the science used to evaluate them will play a critical role in shaping the future of healthcare."

Enable Injections: Transitioning Therapies from IV to SC Administration

Misconceptions remain in the volume that can be delivered subcutaneously, but recent regulatory approvals of on-body injectors, such as those based on the enFuse® On-Body Delivery System, demonstrate how far the industry has progressed, validating that these technologies can support SC delivery of complex biologics in large volumes for

The enFuse® On-Body Delivery System was designed to streamline drug delivery through a compact, wearable injector and transfer system (Enable Injections).



commercial use, including in oncology. Reformulating IV biologic drugs into patient-friendly subcutaneous drugs without introducing unnecessary complexity can also be a challenge. Enable Injections' focus has been on developing a simple, mechanical platform that can help make the transition from IV to SC delivery while maintaining an intuitive experience for patients.

"The enFuse platform includes the flexibility of delivering 5-25mL in a single device, which eases formulation challenges for biopharma," explains Jenn Beeson, Manager, Corporate Communications, Enable Injections. "It also utilizes an original container closure system further streamlining the process and reducing development costs. Enable's commercially available on-body injector is intentionally simple, mechanical, and battery-free, minimizing complexity during drug administration."

Enable is now developing the enFuse Connected Digital System, which will add connected capabilities such as onboarding support, treatment reminders, administration guidance, symptom tracking, and automated data capture, without changing the core

injection workflow. Ms. Beeson says: "The goal is for connected technology to support the injection experience rather than complicate it, by delivering meaningful information to patients and providers, and potentially as a data source in clinical trials."

One example is the recent FDA and EU approval for the CirCLIQ® injector for use with Sanofi's Sarclisa® with multiple myeloma. The program demonstrates how an on-body delivery system can help support conversion from IV administration while providing patients with a simplified subcutaneous option. For pharmaceutical companies, it illustrates how established delivery platforms may be able to reduce

development risk by leveraging technology that has now been validated through multiple regulatory approvals, she says.

"Beyond expanding treatment options, transitioning appropriate therapies from IV to subcutaneous administration has the potential to improve healthcare efficiency by reducing infusion chair utilization and simplifying care delivery," says Ms. Beeson.

Lifecore: Supporting Options for Improved Adherence & Outcomes

Lifecore is seeing a new wave of drug delivery technologies that are enabling higher concentrations, more viscous formulations, and sustained or targeted release profiles – ultimately broadening the range of therapies that can be delivered effectively outside of traditional care settings, says Mary Evelyn Hudson, Director of New Business Development, Lifecore.

At the same time, she says biopolymer materials, such as hyaluronic acid (HA), continue to play an increasingly important role. "HA isn't new – we've been producing pharmaceutical-grade HA for research and commercial product formulations since the 1980s," she notes. "But its versatility, particularly in cross-linked or

Proven approaches and emerging innovations are converging to offer new injectables options to patients (Lifecore).



structured formulations, makes it a powerful platform for controlled and sustained delivery. Because it naturally degrades in the body, it provides a biocompatible way to modulate how therapies are released over time, which is incredibly valuable as therapies become more complex.”

Just as important is how these innovations are working together with established delivery formats. The role of prefilled syringes and autoinjectors is expanding significantly. “As device technologies advance, especially with the ability to handle larger volumes and more viscous formulations, they’re becoming a critical bridge between complex drug formulations and patient-friendly, at-home administration.”

She adds: “What’s most compelling to me is that it’s not any one of these elements alone – it’s the combination. When you bring together advanced delivery technologies, biopolymer-based formulations, and evolving autoinjector platforms supported by prefilled syringes, you effectively expand the aperture of what can be delivered and how. Therapies that may not have been feasible in the past can now reach patients in more accessible, convenient ways, improving adherence and overall outcomes. That convergence – where proven approaches meet emerging inno-

vation – is where I see the greatest momentum and the most compelling opportunities ahead.”

Mitsubishi Gas Chemical Company, Inc.: Multi-Layer Vials Prevent CO₂ Permeation

Cell/Gene therapy (CGT) products have become increasingly popular. As they are stored at harsh conditions such as deep-cold or cryogenic temperatures, it is challenging to use conventional glass vials. As an alternative to glass, Mitsubishi Gas Chemical Co., Inc. developed multi-layer plastic vials suitable for the CGT products.

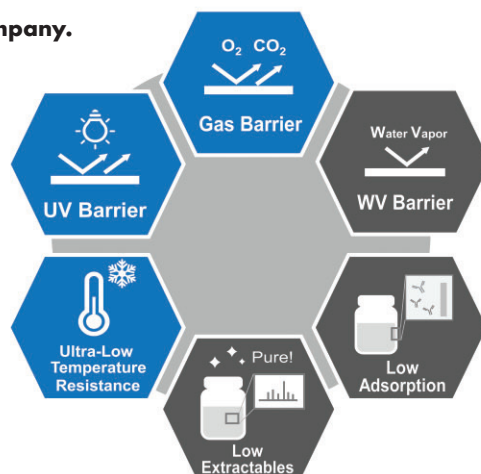
Tomohiro Suzuki, Associate General Manager, Mitsubishi Gas Chemical, says that Cyclic Olefin Polymer (COP) vials are usually used for CGT products, but don’t have sufficient gas barrier properties. “This is a particular issue as new modalities are stored with dry ice generating CO₂ gas, so high gas barrier properties are required for the primary containers,” he says. “Our multilayer plastic vials that can prevent CO₂ permeation were developed based on the demands of our pharma clients.”

PCI: Complex Biologics Paired with Sophisticated Delivery Systems

One of the biggest challenges in injectable delivery today is managing the increasing complexity of drug-device combination products, balancing batch sizes from large commercial volumes to rare/ultra-rare small volumes, while maintaining speed to clinic and speed to market. The rapid growth of biologics, high-concentration formulations, and patient-centric delivery systems means companies must simultaneously address formulation development, sterile manufacturing, device integration, regulatory requirements, and global supply chain considerations – all while reducing development timelines.

PCI addresses this challenge through an integrated approach that combines device assembly, packaging, analytical services, and sterile fill-finish in one organization. “By bringing these capabilities together, we help clients reduce hand-offs between vendors, mitigate program risk, and streamline the path from clinical development through commercialization,” says Paul Smallman, Senior Director, Global Technical Sales, PCI. “Our teams work closely with customers to evaluate formulations, device selection, assembly processes, human factors considerations,

OXYCAPT™ Multilayer Plastic Vial from Mitsubishi Gas Chemical Company.



and packaging configurations early in development. This proactive approach helps identify potential issues before they impact timelines or regulatory submissions.”

In parallel, the global sterile manufacturing and packaging network provides the scalability and flexibility needed to support emerging biotech companies and large pharmaceutical organizations as product demand evolves. Sustainability has become an increasingly important consideration across the pharmaceutical industry, and PCI works closely with clients to identify opportunities to reduce environmental impact without compromising patient safety, product quality, or regulatory compliance.

“Within our device assembly and packaging operations, we support initiatives aimed at reducing material usage, improving packaging efficiency, and minimizing waste throughout the manufacturing process,” he says. “This includes evaluating packaging designs that optimize material consumption, reduce transportation volume, and improve overall supply chain efficiency. We also partner with customers and suppliers to explore more sustainable packaging materials where appropriate and feasible within the regulatory framework governing combination products.”

In addition, PCI continuously invests in operational improvements that enhance energy efficiency, reduce waste generation, and support responsible resource management across its global networks. These efforts are aligned with broader sustainability goals while maintaining the rigorous quality standards required for injectable therapies.

“While sustainability remains an important objective, every decision must also maintain product quality, sterility assur-

ance, patient safety, and regulatory compliance,” says Mr. Smallman. “Our goal is to help clients achieve both environmental and operational benefits without compromising the performance of their injectable therapies.”

Looking ahead, he says that what is most exciting is the convergence of advances in pharmaceutical development, drug manufacturing, and delivery device technologies. “We are seeing increasingly complex biologics, high-value specialty therapies, and novel formulations being paired with sophisticated delivery systems designed to improve the patient experience and support self-administration,” he says. “As biologics, specialty medicines, and personalized therapies continue to expand, we are seeing increasing demand for advanced autoinjectors, wearable injectors, and other delivery platforms that simplify administration while supporting adherence.”

At the same time, advances in connected health technologies are creating opportunities to integrate digital capabilities into injectable delivery systems. The ability to capture treatment data, support adherence monitoring, and provide real-time insights could further enhance patient engagement and outcomes. From a manufacturing perspective, PCI sees progress in automation, data analytics, and integrated supply chain solutions that can improve efficiency and product quality while accelerating commercialization timelines.

Phillips Medisize: Making Home-Based Treatments More Accessible

A growing challenge in injectable delivery is the growing complexity of biologic therapies, which increasingly require

higher viscosities, larger delivery volumes and reliable administration outside traditional clinical settings. This creates a need for devices that are simple and intuitive for patients to use at home while still ensuring accurate, controlled and safe drug delivery. Phillips Medisize is addressing this through a suite of device and technology solutions designed to match different drug and administration requirements, including the Aria™ reusable autoinjector platform, drug delivery solutions for larger volumes, dual-chamber technologies for lyophilized or liquid-liquid formulations, and large-volume infusion technologies.

In the case of one client, Zia Afreedi, Senior Manager, Technical Business Development, Phillips Medisize, explains that there was a need to deliver a long-acting therapy reliably and in the comfort of the home, while keeping the sensitive molecule stable. “Children needing this growth hormone therapy faced daily injections that frequently led to poor adherence — driven by injection pain, bruising and fear of needles,” he explains.

In collaboration with the client, Phillips Medisize developed the SKYTROFA® Auto-Injector – a reusable, rechargeable electromechanical device built around a single-dose, dual-chamber cartridge that holds the freeze-dried drug in one chamber and water in the other. The device automatically reconstitutes the drug, guides a controlled mixing step and delivers the dose after needle insertion, with built-in electronics confirming a full dose.

That transition from clinic to home is being supported by advancements in device technology and artificial intelligence and creating an opportunity for injectable delivery systems to improve adherence and the patient experience. “We are most

excited about the continued shift from intravenous to subcutaneous administration, because that shift can make home-based treatment more accessible, convenient and patient-friendly,” says Mr. Afreedi. “As more therapies are formulated at higher concentrations, smaller delivery volumes may become possible, enabling more compact and discreet injection devices. Conversely, some formulations will be more difficult to administer through traditional means, requiring devices with greater flexibility and delivery control.”

Portal Instruments: Closed-Loop Technology Manages Delivery Parameters Throughout Injection

To keep pace with the evolution of biologic therapies, drug developers are increasingly working with larger-volume and higher-viscosity formulations, while patients and providers continue to seek more convenient treatment options outside traditional healthcare settings.

“The industry is responding by rethinking how delivery systems are designed,” says Patrick Anquetil, PhD, Chief Executive Officer, Portal Instruments. “At Portal Instruments, we believe closed-loop, software-controlled delivery platforms represent an important step forward because they offer greater flexibility, precision, and control than purely mechanical approaches. As therapies continue to evolve, towards higher volumes (5 mL and above) and viscosities (20 cP and above), delivery technologies must evolve alongside them.”

Closed-loop, software-controlled technology continuously monitors and manages key delivery parameters throughout the injection process. At Portal Instruments, this philosophy is reflected in PRIME Nexus™, a software-controlled drug



Portal Instruments' PRIME NEXUS™ is engineered to deliver what conventional spring-based injectors cannot. Its closed-loop, software-controlled architecture continuously adjusts injection parameters in real time, enabling consistent delivery of 5.5mL through a 27-gauge needle in under 20 seconds across a broad range of viscosities.

delivery platform. “The advantage of intelligent delivery systems is their ability to adapt to the specific requirements of a therapy rather than relying on a one-size-fits-all approach,” explains Dr. Anquetil. “By using feedback and control throughout the injection process, closed-loop systems can help support greater consistency, improve the user experience, and provide greater confidence that therapies are being delivered as intended.”

Portal Instruments is currently collaborating with a leading biotechnology company developing next-generation biologic therapies with demanding delivery requirements. As their formulation and clinical strategy evolved, they faced a common industry challenge: how to reliably deliver larger-volume biologics sub-

cutaneously while maintaining a patient-friendly experience. “Using the PRIME NEXUS platform, we demonstrated the ability to deliver a 5.5mL biologic through a 27-gauge needle in less than 20 seconds,” he says. “This is a performance that is difficult to achieve with conventional mechanical autoinjectors. NEXUS accomplishes this through a closed-loop-controlled architecture that continuously monitors and adjusts delivery parameters in real time, ensuring consistent injection performance across varying drug viscosities and container formats.”

For the partner, this created optionality. Rather than being constrained by the limitations of traditional injection devices, they could continue advancing their therapeutic program while evaluating a broader

range of formulation and delivery strategies. More broadly, Dr. Anquetil says this illustrates how next-generation drug delivery technologies can help biopharmaceutical companies bring complex biologics closer to the patient's home and reduce dependence on infusion-based administration.

Stevanato Group: Bridging the Gap to Deliver Combination Products

A key challenge in injectable delivery is bridging the gap between increasingly complex drug formulation requirements and the performance limits of delivery systems. Pharmaceutical companies are developing increasingly complex biologics and advanced therapeutics, while transitioning therapies from intravenous to subcutaneous administration. These trends drive higher drug payloads, often requiring high-concentration formulations, larger injection volumes, or both. This, in turn, creates new demands for combination products that ensure compatibility between formulation, primary container, and delivery device, while delivering reliable performance, usability, and manufacturability at scale.

"At Stevanato Group, we help bridge this gap through an integrated approach that combines drug containment, delivery systems, and final assembly, hence reducing complexity and supporting pharmaceutical companies in bringing increasingly complex therapies to market," says Antonia Torcasio, DDS Product Portfolio Manager, Stevanato Group.

Stevanato Group incorporates smart technology into injection devices where higher levels of control are required. In Vertiva®, an on-body delivery system for large-volume and extended injections,



connectivity is enabled through Bluetooth® Low Energy to support advanced therapy management. The system combines a reusable controller with a single-use, drug-filled Pod encoded with therapy-specific information through NFC technology. "This ensures that only the correct Pod is activated at any given time, helping prevent errors such as the use of incorrect or previously used Pods," she says. "Ultimately, this approach improves reliability and strengthens confidence for both patients and healthcare providers."

Stevanato Group also approaches design through a sustainability lens. Ms. Torcasio says Stevanato Group favors the reuse of electronics to reduce overall waste, as demonstrated by the Vertiva on-body delivery system, which incorporates a reusable controller. The company also offers single-use products with efficient designs, such as the Aidaptus® autoinjector, which can accommodate multiple syringe formats and fill volumes within the same form factor, helping to reduce the number of SKUs during clinical development or when managing multiple drug assets.

She adds that to give customers greater flexibility in their sustainability strategies, Stevanato Group recently intro-

duced the Deora™ fixed-dose pen injector. As a multi-use device, it enables repeated administrations of fixed doses, reducing the number of devices required per therapy and offering a more sustainable alternative to single-use autoinjectors.

West: Innovation to Support Next-Generation Molecules

Balancing the needs of drug developers with the goal of making therapies as patient friendly as possible is a big challenge. Self-administered combination products, such as prefilled syringes and autoinjectors, give patients greater autonomy and support a homecare environment. However, they also introduce additional complexities for drug/device development teams. As therapies move from intravenous infusion to subcutaneous delivery, formulators often face issues like higher viscosity and larger dose volumes. At the same time, the regulatory pathway for combination products can be more complex, which may discourage early adoption of these formats.

"The core challenge is ensuring that life-saving molecules reach patients quickly while still being delivered through

The West Synchrony™ S1 prefillable syringe system uniquely integrates the syringe barrel, plunger, and needle shield/tip cap into a fully harmonized, verified system from a single supplier.



excited by the innovation happening to better support next-generation molecules. “I think we are right on the cusp of some really meaningful advances. Whether it is new formulation approaches that enable higher volume subcutaneous delivery, or a deeper understanding of what patients need in terms of injection tolerability and experience, there is a real opportunity to improve how therapies are delivered.”

Reference

1. Eli Lilly's New \$299 Month-Long GLP-1 Injector Shows Why It's Winning the Weight-Loss Race, by Leila Sheridan, Inc., Feb. 23, 2026.

systems that support ease of use and independence,” says Katie Falcone, Director, Technical Services, Integrated Systems, West. “To address this, the industry must prioritize earlier integration of device and formulation development, leverage platform delivery technologies, and enable greater transparency in data sharing early in development to reduce risk in later stages.”

By simplifying development and designing with the end user in mind, The West Synchrony™ S1 prefillable syringe system helps accelerate timelines without compromising the patient experience, she adds. The West Synchrony S1 PFS system integrates the syringe barrel, plunger and nee-

dle shield/tip cap into a fully harmonized, verified system from a single supplier.

“Unlike traditional component-driven approaches, West Synchrony PFS System delivers a fully verified system-level solution designed specifically for biologics and vaccines,” says Ms. Falcone. “It sets a new standard in drug delivery by accelerating syringe selection through its comprehensive performance and regulatory data packages. This novel approach enables pharmaceutical companies to streamline design, accelerate regulatory submission, and secure a reliable supply chain for combination products that meets quality and volume needs.”

Looking to the future, Ms. Falcone is

Drug Development EXECUTIVE



Patrick Anquetil, PhD

Chief
Executive Officer

Portal Instruments



Steven Kaufman

Chief
Commercial Officer

Portal Instruments



Portal Instruments: Beyond
Springs – Portal Prime
Nexus™ Autoinjector is
a Versatile Solution for
Biologics

Portal is hoping to redefine how biologic medicines are delivered. As therapies become larger, more viscous and more complex, the company believes drug delivery must evolve from fixed mechanical systems to intelligent software-controlled platforms. Patrick Anquetil, PhD, Chief Executive Officer, and Steven Kaufman, Chief Commercial Officer, Portal Instruments, tell *Drug Development & Delivery* that the future of drug delivery is software-defined. As biologics become larger, more viscous and more complex, software offers a fundamentally better way to control and optimize delivery. Prime Nexus™ was built around that philosophy.

Q: How has your business evolved and adapted to the growth of at-home injections?

PA: Actually, the success of GLP-1 devices really helped Portal for a number of reasons. In the past, globally, we were looking at hundreds of thousands to up to tens of millions of devices in terms of devices used by patients for one therapy in a typical year. GLP-1 therapies fundamentally changed expectations around self-injection. They normalized at-home biologic delivery, dramatically increased device volumes, and brought sustainability into the spotlight. First, this created broader awareness about how to use autoinjectors and pen injectors safely at home or when on the go and improved patient compliance. However, when people started to do the math and realized we were disposing of a significant number of used devices, many started to ask for solutions that had less of an environmental impact. We fully support the use of disposable devices for their convenience. As new therapies move toward higher volumes, longer dosing intervals and more viscous formulations, the limitations of conventional spring-powered devices become more apparent. Further, we have seen more interest from therapies beyond GLP-1 for 2.25mL PFS and 5.5mL PFS-based devices. By using our extensive software and hardware experience we were able to move quickly to provide solutions.

Q: Why is injection time a challenge for some devices and why is the range of primary containers, volumes and viscosities such an issue?

SK: In the past, most injectables had a viscosity measured in cP value that was low or much like water. Many traditional autoinjectors start to see potential issues once you go above 20cP due to the nature of using springs as the power source in mechanical devices. There are exceptions which are clever but for many that is the reality. Now, we see volumes of 5-10mL that need to be injected and many of those injectables are also viscous. This is an interesting challenge for the industry in terms of timing. One way is to go with an on-body delivery system (OBDS) and some device companies are already promoting spring-based autoinjector systems for the higher volumes. At Portal, we believe that our device allows for tighter control of the injection times and can help to adjust to these higher volumes and viscosities. My concern is maintaining an allowable hold time for patients when using an autoinjector as we are hearing from biotech/pharma about issues with spring-force profiles: maintaining consistent delivery performance becomes increasingly challenging as force requirements rise. Precise time control is a distinct advantage in the technology we are preparing for our upcoming clinical study with a biotech partner in early 2027 using a well-known 5.5mL PFS.

Q: How does Prime Nexus™, Portal's latest device offering, fit in with the trend towards sustainability?

PA: For us, it is a logical fit. Sustainability is becoming an important design criterion, not just for patients, but also for healthcare systems and pharmaceutical companies. With a reusable device such as Prime Nexus™ having a usable lifetime of up to three years we see advantages over traditional spring-based devices and OBDS for a number of reasons. First, the Prime Nexus™ cassettes which hold our primary containers are made with minimal components and no metal parts vs some autoinjectors and pen injectors that have up to 15 components. Second, it is the cost per injection. By utilizing a reasonably priced reusable autoinjector and a lower cost cassette we are seeing the economics work for the first time. We can compete with the pricing of other device therapies on a per patient injection after a number of months, and be as effective, or even more effective, in delivering the injection and with the added benefit of being more sustainable.

Q: How has your company addressed the challenge of introducing your new technologies to a conservative industry?

SK: The industry is appropriately cautious because patient safety comes first. However, when a new technology clearly solves an unmet need, adoption can happen remarkably quickly. Over the

years, we have seen the move from 1mL to 2.25mL PFS autoinjector, the introduction of OBDS and more. Now, we are seeing a stronger move towards 5 and even 10mL PFS autoinjectors. The typical route for us is to target speaking with key biotech/pharma companies that are facing challenges with their injectables and to spend time with their knowledgeable device landscaping and formulation teams. If there is a potential fit we move to feasibility studies using their primary containers with placebo or drug product to prove out the suitability of Prime Nexus™ to overcome these challenges. Working with great device partners like Gerresheimer and others really helps us to extend our reach globally. Then, if all goes well, and there is also a good cultural fit, we move to signing co-development programs with our platform to ensure readiness for clinical development and eventually commercial production.

Q: Why have electromechanical autoinjectors not been adopted as quickly as simple mechanical devices?

SK: I think this comes down to economics, supply chain and regulatory pathway, as well as maturity of the technology. Such devices need to be cost competitive. Full stop. If they are truly enabling, some price premium is acceptable, but at the same time biotech/pharma need to be able to put forward a business model that makes sense. For the supply chain we have to ensure we can demonstrate the robustness of the materials that are used in these devices and have alternate suppliers for key components to risk mitigate, especially after covid and taking into consideration other geopolitical factors. And, in the past, there was an assumption that it was much more difficult to achieve approval for electromechanical devices from a regulatory point of view. Now with similar OBDS devices approved and soon to be approved we need the market more accepting of electromechanical devices, especially with new autoinjectors like Prime Nexus™ coming to market.

Q: What is next for Portal?

PA: We are focused on supporting our existing partners as they move toward clinical development while expanding collaborations with additional pharmaceutical companies. But the bigger opportunity extends beyond any individual program. We believe the industry is at an inflection point. As biologics become larger, more viscous and more complex, drug delivery must become intelligent as well. Prime Nexus™ represents that next generation, a software-defined platform designed not simply for today's therapies, but for tomorrow's medicines. ♦

REGULATORY COMPLIANCE

Navigating ISO 23908:2024 & EN ISO 23908:2025 Harmonization: What It Means for Your Combination Product Strategy

By: Murtaza Rana and Aurélie Rebuffet

INTRODUCTION

Sharps injury prevention remains an important consideration for needle-based medical devices and drug-device combination products. With the publication of ISO 23908:2024,¹ expectations for sharps injury protection mechanisms have been updated to reflect a broader scope, stronger risk-management principles, and more explicit usability and performance testing requirements. For pharmaceutical and device manufacturers, the revised standard is an opportunity to reassess how sharps injury risks are addressed across product development, regulatory submissions, and lifecycle management.

They may also be categorized as either active, requiring a specific user action to engage the protection mechanism, or passive, activating automatically without additional user intervention.

ISO 23908 provides a framework for assessing the effectiveness of SIPMs. Specifically, it evaluates whether the mechanism:

- Activates as intended
- Achieves and maintains a safe state
- Prevents accidental access to the sharp following intended use
- Minimizes exposure risk during disposal or recovery

Importantly, ISO 23908 is focused on the performance and usability of the sharps injury protection mechanism itself. Compliance with the standard does not replace the need to evaluate the overall safety, performance, effectiveness, or applicable regulatory requirements of the medical device or drug-device combination product in which the SIPM is incorporated.

WHAT IS THE ISO 23908 STANDARD?

ISO 23908 is an international standard published by the International Organization for Standardization (ISO) that defines requirements and test methods for evaluating the performance and usability of sharps injury protection mechanisms (SIPMs). SIPMs are used with devices containing a needle or other single-use sharp intended for the administration and/or extraction of blood, body fluids or medicinal substances.

The standard aims to minimize the risk of accidental sharps injuries from contaminated sharps after intended use, including during handling, disposal, and, where applicable, recovery. SIPMs may be integrated into the device or provided as stand-alone components that are assembled with the device prior to use.

WHAT IS NEW IN THE 2024 VERSION?

ISO 23908:2024 supersedes the 2011 edition, but is not a complete departure from the original standard. The 2011 version established key principles for sharps injury prevention, including risk-based design, simulated use testing, and active or passive SIPMs. Building on this foundation, the 2024 revision expands the scope of the standard and provides greater clarity regarding performance expectations, testing methodologies, usability considerations, foreseeable misuse, and product lifecycle aspects.

Key enhancements introduced in the ISO 23908:2024 include:

- Broadened scope to explicitly include medical substance administration;
- Stronger alignment with current risk management and usability engineering standards (ISO 14971:2019 and IEC 62366-1:2015+Amd1:2020, respectively);
- More explicit consideration of foreseeable misuse for active protection mechanisms;
- Introduction of a free-fall test to assess protection following accidental dropping;
- Addition of a 5N challenge to assess access to the sharp in safe mode;
- Updates to certain statistical and test-method expectations;
- Consideration of recovery, where applicable, as an element of product lifecycle.

In practical terms, the 2024 revision reinforces the expectation that SIPMs not only activate as intended but also maintain their protective function throughout post-use handling, transport, disposal, and, where relevant, recovery processes. This evolution is particularly relevant for drug-device combination products, where

safety, usability, risk management, and regulatory expectations are increasingly interconnected and must be addressed holistically throughout the product lifecycle.

US REGULATORY CONTEXT

The FDA has recognized ISO 23908:2024 and will continue to accept declarations of conformity to ISO 23908:2011 until July 4, 2027. After that date, declarations to the 2011 edition will no longer be accepted for relevant pre-market submissions²

FDA’s 2005 guidance on medical devices with sharps injury prevention³ features emphasizes the importance of design controls, risk analysis, bench testing, simulated clinical use testing, sterilization, biocompatibility and labelling. The guidance further clarifies that it applies to the sharps injury prevention feature and does not replace device-specific guidance applicable to the underlying device.

For manufacturers, ISO 23908:2024 should therefore be applied as part of a broader regulatory strategy that also considers relevant FDA guidance, recognized consensus standards and product-specific regulatory requirements.

EU HARMONIZATION: STATUS AND IMPACT

ISO 23908:2024 was adopted by the European Standards Organization (CEN) as EN ISO 23908:2025 in August 2025 and subsequently published by national standards bodies across Europe (e.g. BSI, DIN, DS, and NEN). On June 11, 2026, EN ISO 23908:2025⁴ was cited in the Official Journal of the EU (OJEU), thereby becoming a harmonized standard under the EU Medical Device Regulation (EU MDR - Regulation (EU) 2017/745).

In Europe, harmonized standards play an important role in demonstrating conformity with EU directives or regulations. Annex ZA of a harmonized European standard serves as the link between the technical requirements of the standard and the General Safety and Performance Requirements (GSPRs) of the EU MDR. It demonstrates that compliance with the standard provides a “presumption of conformity” with the corresponding legal requirements. i.e. Compliance with a harmonized standard indicates that requirements of the applicable EU directive or regulation are met.

For EN ISO 23908:2025, Annex ZA⁵ identifies a relationship with GSPRs 11.1 and 22.2 of the EU MDR, both of which include requirements to reduce, as far as possible and appropriate, the risks associated with needle-stick injuries:

TABLE ZA.1		
Table ZA.1 — Correspondence between this European standard and Annex I of Regulation (EU) 2017/745 [OJ L 117]		
General Safety and Performance Requirements of Regulation (EU) 2017/745	Clause(s) / subclause(s) of this EN	Remarks / Notes
11.1 a) and b)	5.1.1, 5.1.2, 5.1.3, 5.1.4, 5.1.5, 5.1.6, 5.2, 5.3	Covered provided that the SIPM is integrated as part of the device before use, including any required pre-use assembly.
22.2	5, 6, 7	Covered provided that the SIPM is integrated as part of the device before use, including any required pre-use assembly.

EU MDR GSPRs 11.1 AND 22.2

• **Annex I, Point 11.1:** “Devices and their manufacturing processes shall be designed in such a way as to eliminate or to reduce as far as possible the risk of infection to patients, users and, where applicable, other persons. The design shall: reduce as far as possible and appropriate the risks from unintended cuts and pricks, such as needle stick injuries; allow easy and safe handling; reduce as far as possible any microbial leakage from the device and/or microbial exposure during use; and prevent microbial contamination of the device or its content such as specimens or fluids.”

• **Annex I, Point 22.2:** “Devices for use by lay persons shall be designed and manufactured in such a way as to: ensure that the device can be used safely and accurately by the intended user at all stages of the procedure, if necessary after appropriate training and/or information; reduce, as far as possible and appropriate, the risk from unintended cuts and pricks such as needle stick injuries; and reduce as far as possible the risk of error by the intended user in the handling of the device and, if applicable, in the interpretation of the results.”

The harmonization of EN ISO 23908:2025 may therefore increase scrutiny of devices that incorporate exposed sharps without a sharps injury protection mechanism (SIPM). Manufacturers should be prepared to justify how such devices satisfy the applicable GSPRs and achieve an equivalent level of safety.

The implications extend beyond CE-marked medical devices. Through Article 117 of Regulation (EU) 2017/745, manufacturers of integral drug-device combination products (iDDCs) must obtain a Notified Body opinion for certain new marketing applications and significant product changes. In performing these assessments, Notified Bodies are expected to consider relevant harmonized standards as part of their evaluation, regardless of whether compliance is explicitly claimed by the manufacturer.

It is important to note that the use of harmonized standards remains voluntary. However, when a manufacturer elects not to apply a harmonized standard, it must demonstrate – through a robust scientific and technical justification – that its alternative approach satisfies the applicable MDR requirements and provides an equivalent level of safety and performance.

As a result, manufacturers of iDDCs containing exposed sharps, such as pre-

filled syringes with staked needles and no integrated SIPM, should carefully assess the impact of EN ISO 23908:2025 on future submissions and lifecycle changes. In the absence of compliance with the standard, additional justification may be required to demonstrate conformity with MDR requirements related to sharps injury prevention.

HOW CAN MANUFACTURERS ACHIEVE COMPLIANCE?

One approach to addressing the requirements of the revised standard is to incorporate a sharps injury protection mechanism (SIPM) that complies with ISO 23908:2024/EN ISO 23908:2025 into the existing prefilled syringe presentation. BD offers the BD UltraSafe Plus Passive Needle Guard, an integrated SIPM designed to meet the requirements of ISO 23908:2024 and EN ISO 23908:2025.

Because the primary container and drug-contacting components of the prefilled syringe remain unchanged, the regulatory and development impact can be significantly reduced compared with the introduction of a new primary container system. This may reduce the extent of new supporting data required for primary

packaging materials. As a result, implementation timelines can be substantially shortened.

To support development activities, BD can provide compatibility data demonstrating the use of BD UltraSafe Plus™ with compatible ISO 11040-4:2024⁶ glass syringe barrels. In addition, human factors and usability data are available to help demonstrate the safe and effective use of this widely adopted device platform.

WHAT IS THE REGULATORY IMPACT OF ADDING A SECONDARY DEVICE?

The addition of an integrated needle safety device to an approved drug-device combination product is typically considered a significant change and therefore requires regulatory assessment. For products marketed in Europe, the addition of a SIPM would generally require:

- A new or updated Notified Body Opinion (NBOP) under Article 117, reflecting the modified device constituent part; and
- Submission of a Type II variation (Q.IV.2(a)) to obtain approval of the revised product presentation.

While actual review timelines vary depending on the product, regulatory pathway, and health authority workload, manufacturers should anticipate that the combined approval process may take approximately 12 months from submission to implementation.

Despite these regulatory requirements, adding a compliant SIPM can provide a practical pathway to addressing evolving sharps injury prevention expecta-

tions while leveraging the existing drug product, primary container, and supporting data package.

CONCLUSION

The publication of ISO 23908:2024 and its subsequent adoption as EN ISO 23908:2025 represent an evolution in the regulatory and technical expectations for sharps injury protection. While the 2024 revision builds upon the well-established principles of the 2011 edition, it introduces more robust requirements related to risk management, usability, foreseeable misuse, performance verification, and lifecycle considerations. New expectations, including free-fall testing, a 5N access-to-sharp challenge, and updated statistical evaluation methods, reflect an increased focus on demonstrating protection under realistic use conditions throughout the product lifecycle.

From a regulatory perspective, the significance of the standard extends beyond technical compliance. In the United States, FDA recognition of ISO 23908:2024 reinforces its relevance within regulatory submission strategies. In Europe, the harmonization of EN ISO 23908:2025 under the EU MDR provides a presumption of conformity with key GSPRs related to needle-stick injury prevention, making the standard an important consideration during Notified Body assessments of both medical devices and integral drug-device combination products.

Although compliance with harmonized standards remains voluntary, manufacturers choosing not to apply EN ISO 23908:2025 should be prepared to provide a robust scientific and technical justification demonstrating an equivalent level of safety and performance. This may present increasing challenges for products that incorporate exposed sharps without an integrated sharps injury protection mechanism.

For manufacturers seeking a practical path forward, the integration of a compliant SIPM – such as the BD UltraSafe Plus Passive Needle Guard – can help address evolving regulatory expectations while minimizing the impact on the drug product and primary container system. By leveraging existing packaging configurations and available compatibility and usability data, implementation may be achieved with substantially less development effort than a complete container redesign.

Ultimately, manufacturers should proactively assess the implications of ISO 23908:2024 and EN ISO 23908:2025 on both existing products and future development programs. Early eval-

uation of compliance strategies can help reduce regulatory risk, support successful regulatory submissions, and enhance protection for healthcare professionals, patients, and other users who interact with sharps throughout the healthcare ecosystem. ♦

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BIOGRAPHIES



Murtaza Rana is a Senior Regulatory Affairs Manager at BD Medical - Pharmaceutical Systems, where he leads the regulatory affairs team managing syringe safety, pen injector, and autoinjector platforms. With more than 18 years of experience in medical devices, in vitro diagnostics, and combination products, he has extensive expertise in global regulatory submissions, product

development, lifecycle management, and international market access. In his prior role, he was actively involved in regulatory standards initiatives through industry associations and standards committees. He holds Bachelor's and Master's degrees in Biomedical Engineering from the New Jersey Institute of Technology.



Aurélie Rebuffet is a Senior Staff Specialist in Regulatory Affairs at BD Medical - Pharmaceutical Systems. In her role, she defines and implements regulatory strategies, leads complex cross-functional initiatives and represents Regulatory Affairs in strategic projects and international forums. Her work ensures compliance excellence while creating value-driven solutions for

clients and the organization. Dr Rebuffet began her career in Regulatory Affairs at Sanofi Pasteur, before joining BD in 2016. She holds a Doctorate in Pharmacy from Grenoble Pharmacy University (France), a Civil Engineering degree from École des Mines de Saint-Étienne (France), and a Master's degree in Regulatory Affairs from Paris-Sud Pharmacy University (France).

QUALITY MANAGEMENT SYSTEM

One QMS, Four Delivery Platforms: Can Your Quality System Manage Complexity at Scale?

By: Melanie Cerullo

INTRODUCTION

As drug development portfolios expand across multiple delivery platforms, increasing complexity places quality systems under greater strain. For contract development and manufacturing organizations (CDMOs) supporting injectable, inhalation, nasal and transdermal products in parallel, the quality management system (QMS) must do more than ensure compliance. It must provide a coherent framework for decision-making, while maintaining control and enabling scientifically sound, phase-appropriate flexibility.

From my perspective, the differentiator is a quality system that manages risk consistently across platforms. A harmonized QMS, supported by clear governance and strong site-level execution, is essential to de-risk development, accelerate progress and sustain regulatory confidence.

MANAGING A DIVERSIFIED PORTFOLIO WITHOUT FRAGMENTING QUALITY

Modern development pipelines increasingly include complex formulations, combination products and advanced delivery systems, each with distinct critical quality attributes and failure modes. When these products are managed within siloed or platform-specific quality systems, inconsistency becomes inevitable.

Injectable products demand absolute control of sterility, particulates and endotoxins. These expectations are well understood, but complexity increases with long-acting injectables, high-viscosity formulations or turbid products that challenge conventional sterility and particulate testing approaches. Without a disciplined quality framework, method variability and inconsistent risk justification quickly emerge.

Pulmonary and nasal products are drug-device combination products that require coordinated control of formulation, device performance, extractables and leachables, and patient use considerations. For inhalation and nasal delivery, aerodynamic particle size distribution is a critical quality attribute that directly affects dose delivery, placing significant demands on validated, reproducible analytical methods.

Transdermal products present equally demanding challenges that require robust control of formulation stability, uniformity, adhesion and controlled release. Risks such as active substance crystallization, process residue carryover or solvent retention can directly affect performance and patient safety. In practice, these risks often justify controls that go beyond minimum compendial or guideline expectations.

Across all platforms, regulatory expectations are consistent in one respect: quality must be designed into the product and demonstrated through data. A fragmented quality approach cannot reliably meet this standard.

WHY A HARMONIZED QMS IS ESSENTIAL

A unified pharmaceutical quality system provides the backbone for managing complexity by defining how quality decisions are made, documented, reviewed and improved.

Across platforms and sites, deviation management, corrective and preventive action (CAPA), change control, supplier qualification and management review should follow one set of expectations and one workflow. This consistency supports inspection readiness and gives leadership an enterprise-level view of performance and risk, consistent with International Council for Harmonisation (ICH) Q10.

CAPA and change control warrant particular focus because they link day-to-day execution to systemic improvement. When these processes vary by site, issues recur, root cause analysis loses rigor and lessons stay local rather than strengthening the network.

EMBEDDING FLEXIBILITY THROUGH QUALITY RISK MANAGEMENT

While management systems must be standardized, technical execution must remain risk-based. This is where quality risk management, aligned with ICH Q9, becomes essential.

A mature QMS embeds risk management into everyday decision-making. Tools such as failure modes and effects analysis (FMEA) are not treated as one-time exercises, but as living assessments that inform method development, validation strategies, process changes and control selection.

This approach supports phase-appro-

priate analytical strategies, with early clinical programs relying on fit-for-purpose methods that enable speed and learning. As products advance, validation rigor increases in line with patient exposure and regulatory expectations. The QMS defines the framework and governance for these decisions, while risk assessments justify the technical path forward.

This balance between structure and flexibility is where many quality systems fail. Either they over-standardize, slowing development unnecessarily, or they allow excessive local discretion without sufficient governance. Neither of these models is sustainable at scale.

EXECUTION FUNDAMENTALS: DATA INTEGRITY & DEFINED ACCOUNTABILITY

Even the best-designed QMS fails without disciplined execution. Two elements are particularly critical: data integrity and clear accountability between sponsor and CDMO.

A harmonized QMS must enforce consistent computer system validation, access control, audit trails and record retention across all platforms and sites to protect the data integrity that is fundamental to every quality decision. Alignment with global regulatory expectations, including Title 21 of the Code of Federal Regulations Part 11 and ALCOA+ (attributable, legible, contemporaneous, original, accurate, plus complete, consistent, enduring and available) principles, is essential. Without confidence in data, neither sponsors nor regulators can rely on the product.

Equally important are well-defined quality agreements. Sponsors retain ulti-

mate responsibility for product quality, regardless of outsourcing. These agreements must clearly define roles, responsibilities, escalation pathways and decision rights, with appropriate recognition of platform-specific risks. Ambiguity in this area is a common root cause of compliance failures.

GOVERNANCE THAT ENABLES CONSISTENCY & EXPERTISE

A governance model that combines centralized quality oversight with strong, empowered site-level expertise maintains consistency while enabling platform-specific execution.

Central quality functions set standards and ensure regulatory alignment, while site teams execute scientifically and manage platform-specific risk. This balance avoids the pitfalls of over-centralization, which can suppress technical judgment, and over-decentralization, which leads to inconsistency.

This model is particularly important for deviations, CAPA and change control, where common definitions and workflows support consistent execution and comparable performance metrics. When governance is clear, decisions are faster, more consistent and more defensible.

QUALITY SYSTEMS THAT SCALE WITH COMPLEXITY

As development portfolios diversify and technical complexity increases, quality systems must evolve accordingly. A QMS that is siloed, overly localized or inconsistently applied will not withstand regulatory scrutiny or support reliable execution at scale.

A coordinated, risk-based quality system with clear governance provides the foundation for managing multiple delivery platforms without compromising control. When core processes are standardized and risk management is embedded, quality becomes predictable and defensible. Enabling site expertise within defined boundaries makes that performance sustainable.

For sponsors, the expectation should be clear: a CDMO's quality system must do more than meet baseline compliance. It must demonstrate how risk is identified and reduced across the product lifecycle. For CDMOs, this requires disciplined execution, with oversight that drives continuous improvement.

When quality systems are designed to manage complexity rather than react to it, they enable faster development, stronger regulatory outcomes, and, ultimately, consistent delivery of safe and effective medicines to patients. ♦

BIOGRAPHY



Melanie Cerullo is the Chief Quality Officer & Head of Regulatory Affairs at Kindeva. With over 25 years of experience in pharmaceutical manufacturing, regulatory compliance and quality assurance, she brings a deep expertise in developing and executing robust quality systems that ensure patient safety and regulatory excellence to Kindeva. She is responsible for leading Kindeva's global quality, compliance and regulatory strategy. She oversees risk management related to product quality, drives quality training programs and ensures all projects meet or exceed FDA, EMA and ICH regulatory standards. Her leadership will be pivotal in supporting Kindeva's continued innovation and expansion into new therapeutic modalities.

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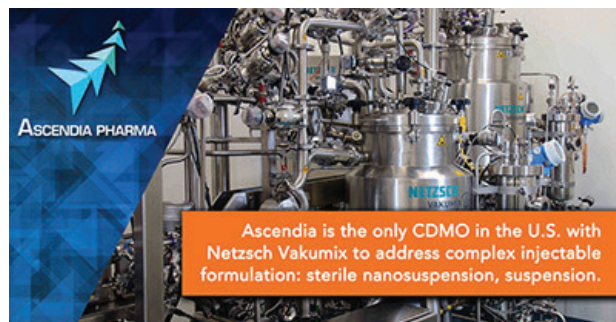
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