Drug Development & Delivery

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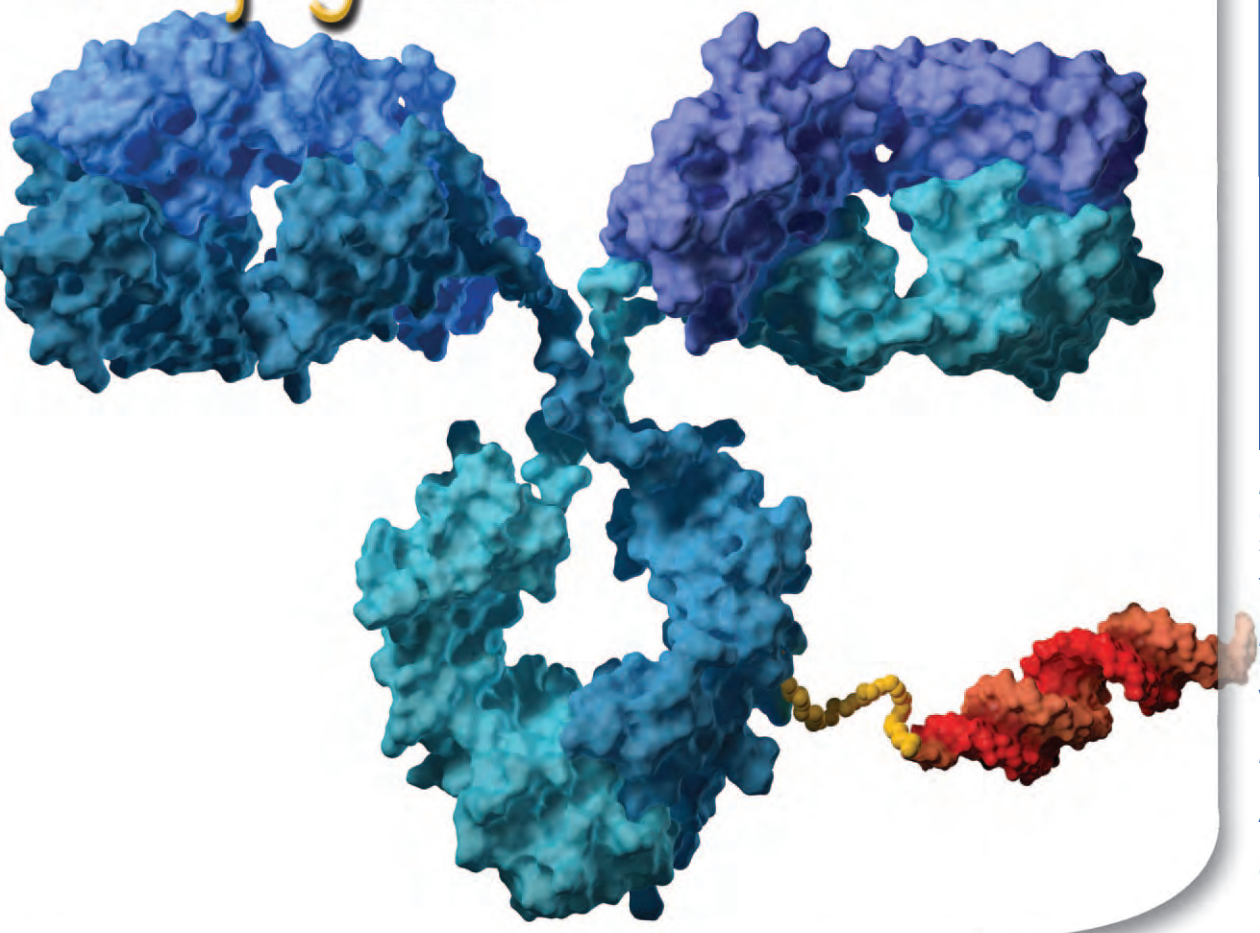
Antibody Oligonucleotide Conjugates



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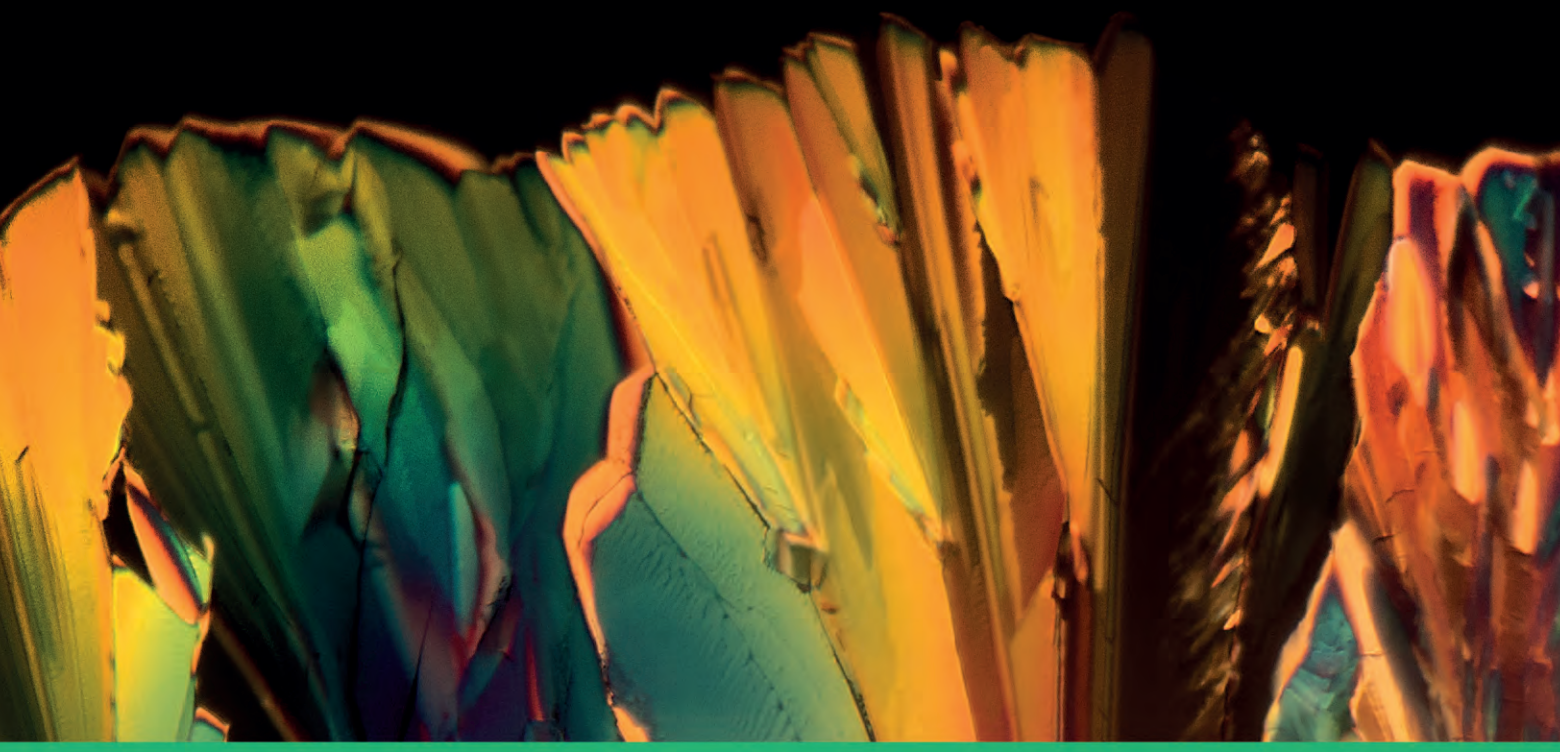

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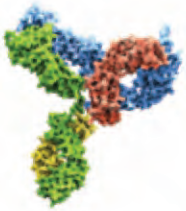
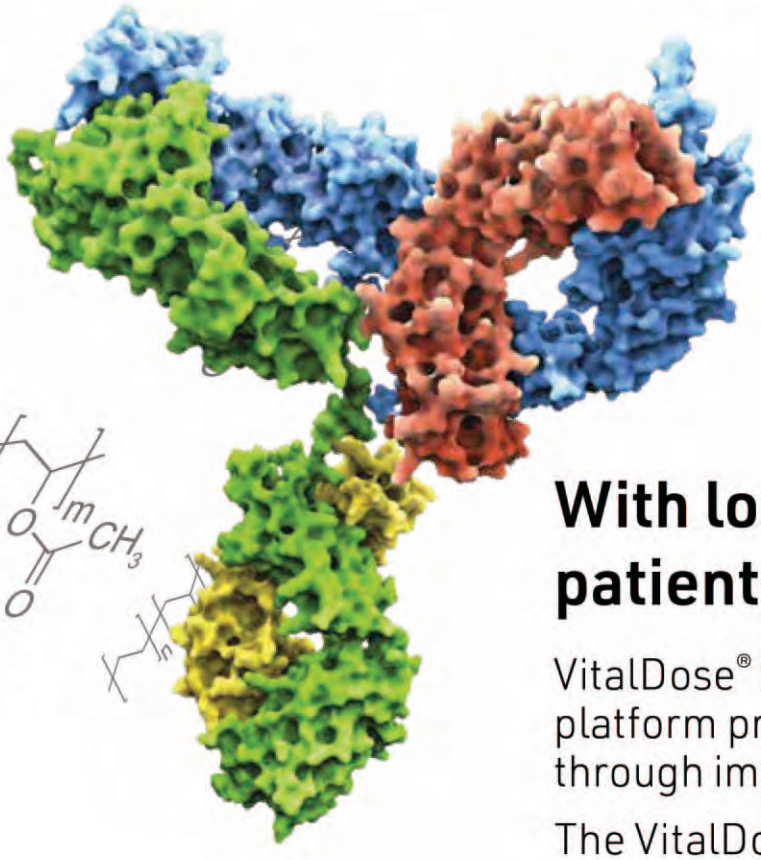
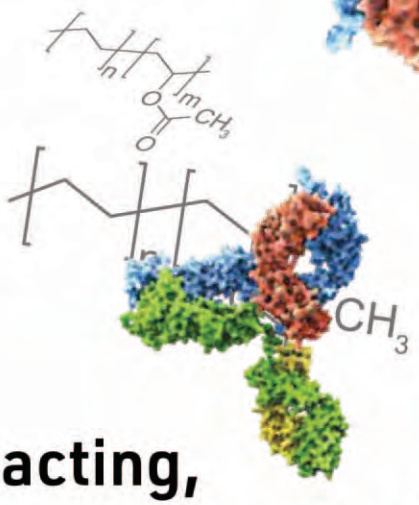
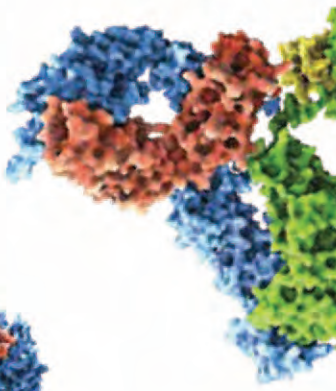


Sustained Drug Delivery







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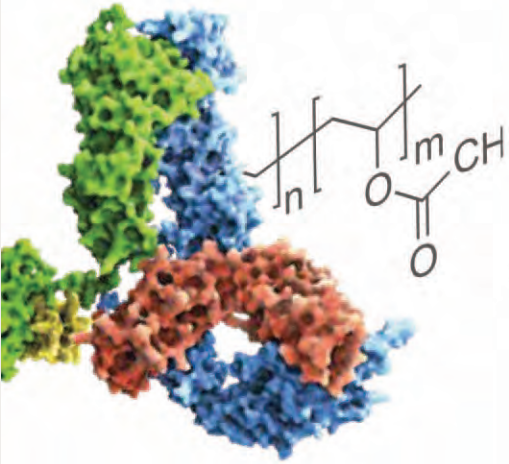

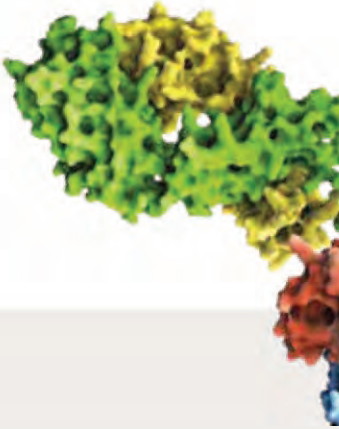

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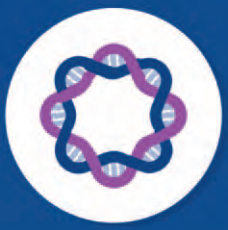

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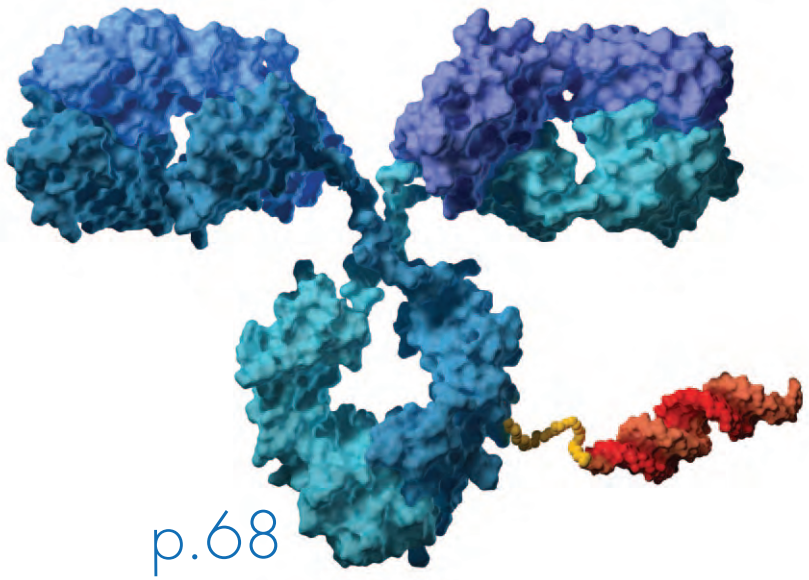
Revolutionizing a New Class

"This revolutionary advancement provides evidence we can overcome a challenge that has eluded scientists for decades – the opportunity to target tissues beyond the liver with RNA therapeutics. This breakthrough milestone was only the beginning."



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Together, delivering life changing therapies | Let's talk future™

ModeX Therapeutics Leverages ProBioGen's Expertise for Accelerated COVID-19 Antibody Development

ProBioGen recently announced a pivotal collaboration with ModeX Therapeutics an OPKO Health Company dedicated to combating cancer and infectious diseases with cutting-edge multi-specific biologics. ModeX has signed a Master Services Agreement with ProBioGen to accelerate the development and production of clinical material of their multi-specific COVID-19 antibody. This strategic fee-for-service collaboration encompasses a full spectrum of services, including advanced cell line development, cutting-edge process optimization, and large-scale GMP production. ModeX will harness the power of ProBioGen's pioneering DirectedLuck Transposase Technology, which enables the production of high-titer, stable expression cell lines that are critical to the success of ModeX's antibody program.

"ProBioGen is thrilled to work on ModeX's fascinating complex COVID-19 antibodies," said Dr. Volker Sandig, CSO at ProBioGen. "Our CHO.RiGHT platform together with the DirectedLuck transposase technology provides the robustness and flexibility to address specific needs of each molecule and create the very best cell line with accelerated time lines. The partnership represents a bold step toward industrial manufacturing of this important drug candidate."

"We are excited to partner with ProBioGen to advance our COVID-19 antibody program," added Dr. Peter Bernhardt, CMC Lead at ModeX. "This collaboration marks a pivotal moment in our mission to deliver transformative therapies for infectious diseases, and we are confident that our combined expertise will drive meaningful progress."

This project has been funded in whole or in part with federal funds from the Department of Health and Human Services (HHS); Administration for Strategic Preparedness and Response (ASPR); Biomedical Advanced Research and Development Authority (BARDA), under contract 75A50123C00056. This funding is part of Project NextGen, an HHS program to accelerate and streamline the rapid development of the next generation of vaccines and therapeutics.

ProBioGen's DirectedLuck transposase system combines an optimized highly active transposase and transposon with epigenetic targeting. It is equipped with a recognition domain for specific histone marks that integrates multiple copies of transgene expression units individually at genomic regions with highest transcriptional activity. As a result, it achieves exceptionally high protein expression and maximum stability in clone pools and clones. This reduces time and manual lab work for selecting superior clones for best titers, proven stability and product quality.

The DirectedLuck Transposase is compatible with genetic elements in standard expression vector design and can be used with host cell lines of different species and tissue origin. DirectedLuck delivers superior cell lines for standard mAbs and complex glycoproteins and provides additional benefits for bispecifics and virus producer cell lines where it allows gradual adjustment of relative expression levels for optimal product quality. DirectedLuck is available for out-licensing. Furthermore, ProBioGen applies DirectedLuck as a standard tool in clients' service projects at no extra charge.

Artelo Biosciences Presents Highly Encouraging Data Toward Developing Solid Dosage Form of ART12.11

Artelo Biosciences, Inc. recently announced Dr. Andrew Yates presented new preclinical data on ART12.11 at the CT-CANN24 conference held May 29-30, 2024, at the Hilton London Canary Wharf in London, UK.

The presentation, titled *An Aqueous Suspension of a Novel Cannabidiol: Tetramethylpyrazine Co-crystal, demonstrates a pharmacokinetic profile comparable with Epidiolex® in Rats*, highlights the company's patented cocrystal of CBD and TMP (tetramethylpyrazine), ART12.11, in an unoptimized formulation, demonstrated comparable pharmacokinetics of CBD and its metabolites to a mimic of Epidiolex, an FDA approved oral solution of CBD in ethanol and sesame oil used for controlling seizures in orphan childhood disorders with over $845 million in net sales for 2023. Oral solutions are commonly used for treating young children; however, for adolescents and adults a solid dosage form is preferred. A tablet form of ART12.11 is expected to be more attractive than an oral solution given its advantages in precise dosing, storage and transport.

Andrew Yates, PhD, Chief Scientific Officer and Senior Vice President of Artelo, said "We are excited to present our first comparative data of ART12.11 versus an Epidiolex-like formulation of CBD to the cannabinoid research community. The data not only shows we can outperform an equivalent formulation of CBD but also that ART12.11 already has comparable CBD levels in plasma provided by Epidiolex. The data we have from both the rat and dog pharmacokinetic studies provide us confidence that we can design an optimized solid-dosage form for the clinic, that will open new frontiers for CBD clinical research in broader populations."

As previously reported, ART12.11 offers improvements in physicochemical, pharmacokinetics, and pharmacodynamic properties compared to CBD. In addition, strong evidence previously announced with ART12.11 in an animal study of stress-induced anxiety and depression showed Artelo's cocrystal composition outperformed CBD with just a third of the amount of CBD in the cocrystal than in the comparator arm of CBD alone. This data highlights Artelo's opportunity to reduce the expected pill burden with its oral solid formulation and the company is currently developing an optimized tablet of ART12.11 for planned clinical studies.

ART12.11 is Artelo's wholly owned, proprietary cocrystal composition of cannabidiol (CBD) and tetramethylpyrazine (TMP). Isolated as a single crystalline form, ART12.11 has exhibited better pharmacokinetics and improved efficacy compared to other forms of CBD in nonclinical studies. Superior pharmaceutical properties, including physicochemical, pharmacokinetic, and pharmacodynamic advantages have been observed with ART12.11. Artelo believes a more consistent and improved bioavailability profile may ultimately lead to increased safety and efficacy in humans, thus making ART12.11 a preferred CBD pharmaceutical composition. The US issued composition of matter patent for ART12.11 is enforceable until December 10, 2038.

Spinogenix Announces FDA Clearance of IND Application Novel Therapy for the Treatment of ALS

Drug (IND) application for its Phase 1/2 clinical trial of SPG302 for the treatment of people with Amyotrophic Lateral Sclerosis (ALS). The trial will evaluate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics of SPG302 dosed as a once-a-day pill in ALS patients.

"Having completed the Phase 1 safety study in healthy subjects in Australia, we are thrilled to have gained FDA acceptance of our US IND for SPG302 in ALS," said Stella Sarraf, PhD, Spinogenix Chief Executive Officer and Founder. "SPG302's unique approach to regenerate synapses offers a fundamentally different treatment modality, focusing on synapse loss, which is central to ALS. Current treatments have not sufficiently met the needs of ALS patients, as slowing disease progression alone is not enough. We are committed to advancing SPG302 with the hope of providing a new, transformative therapeutic that can significantly improve the lives of those battling this devastating disease."

SPG302 has been granted US FDA Orphan Drug Designation (ODD) for the treatment of ALS and has received preclinical support from the US National Institutes of Health (NIH) and the Department of Defense (DoD). SPG302 is currently undergoing a Phase 1/2 study in Australia, which has completed dosing of healthy volunteer cohorts, showing dose proportionality, excellent tolerability and plasma levels aligned with efficacy in animal models. Dosing of ALS patients in Australia began in April 2024. Additional information on the trial may be found on ClinicalTrials.gov (NCT05882695).

Dr. Merit Cudkowicz, Chair of the Massachusetts General Hospital Department of Neurology, Director, Sean M. Healey & AMG Center for ALS at Massachusetts General Hospital, Julieanne Dorn Professor of Neurology at Harvard Medical School, and Spinogenix Advisory Board member, added "ALS is a complex and varied disease, affecting cognitive and motor functions as well as speech and respiration. Spinogenix's new approach works at the synaptic level to regenerate synapses. This first study in people with ALS is an important step towards determining whether SPG302 helps recover lost functions in motor and cognitive symptom domains."

SPG302 is a once-a-day pill being developed as a regenerative treatment for ALS and other neurodegenerative diseases that has the unique ability restore synapses, the key connections between neurons that allow people to think, plan, remember, and control motor functions. The synaptic regenerative activity of SPG302 represents a first-in-class approach to treating ALS and has the potential to reverse declines in cognitive, respiratory, and motor function.

Spinogenix is dedicated to developing transformative therapeutics for conditions involving the loss or dysfunction of synapses. Our lead clinical-stage synaptic regenerative candidate is a first-in-class therapeutic designed to reverse synapse loss and improve cognitive and motor functions in neurodegenerative and neuropsychiatric diseases such as ALS, Alzheimer's disease, and schizophrenia. In parallel, we are also developing a synaptic function therapeutic designed to improve behavior in Fragile X Syndrome.

selectION Announces Initiation of Phase 1b Clinical Trial Evaluating si-544 in Patients With Psoriasis Vulgaris or Psoriatic Arthritis

selectION, Inc. recently announced the initiation of a Phase 1b trial with its lead compound si-544 in adult patients with psoriasis vulgaris (Ps) or psoriatic arthritis (PsA). si-544 is a selectivity-optimized peptide blocking the Kv1.3 ion channel. Kv1.3 is a key target in autoimmunity, which the company believes has the potential to set a new standard for safety and tolerability in the treatment of T cell autoimmunity. Enrollment is ongoing and topline data are expected in the fourth quarter of 2024.

This new clinical study is designed as a multicenter, Phase 1b, double-blind, placebo-controlled trial in adults with mild to severe Ps or PsA. The company anticipates enrolling up to 40 patients with Ps, of which up to 16 patients may also have PsA.

This psoriasis study follows the recent completion of the company's first-in-human Phase 1b trial in atopic dermatitis patients, in which the company observed safety and tolerability of si-544 in adult patients with mild-to-severe atopic dermatitis. The current Phase 1b trial design in patients with Ps or PsA should also allow for the evaluation of efficacy signals. Patients will undergo a 4-week treatment period and a subsequent 12-week follow-up period.

While the primary endpoints of the trial are safety and tolerability, secondary endpoints include the assessment of PD markers such as inflammatory cytokine levels.

Andreas Klostermann, PhD, Chief Scientific Officer and co-founder of the company said "We are focused on expanding clinical development of si-544 in autoimmune indications, and we are looking forward to the results of this second, larger trial in a T cell-driven disorder."

Antonius Schuh, PhD, Chairman and CEO of selectION, Inc. added "The promising data from our successful clinical study in atopic dermatitis patients provide further evidence that direct targeting of disease-associated, chronically activated T cells via Kv1.3 inhibition may provide effective and safe treatments for patients living with a broad variety of autoimmune diseases."

si-544, the company's lead drug candidate, is blocking Kv1.3, a specific ion channel involved in the activation and proliferation of TEM cells, with what the company believes to be class-leading selectivity. TEM cells lie at the root of many autoimmune indications such as atopic dermatitis, psoriasis, rheumatoid arthritis, or multiple sclerosis, but also of certain rare cancers like lymphomas.

si-544 has demonstrated what the company believes is an excellent safety and tolerability profile in a recently completed Phase 1b clinical trial in atopic dermatitis patients, with study results also indicating an initial efficacy signal. Previously, si-544 has demonstrated what the company believes is excellent efficacy in animal and human T cell models.

The compound is a potent immuno-selective agent addressing a significant unmet medical need by functionally inhibiting and eliminating disease-specific, chronically activated TEM cells while maintaining full immunocompetence.

Jeito Capital Announces Acquisition by Merck & Co. of its Portfolio Company EyeBio for a Potential Value of $3 Billion

Jeito Capital recently announced its portfolio company EyeBiotech Limited and Merck & Co. have entered into a definitive agreement under which, Merck & Co., through a subsidiary, will acquire EyeBio. Under the terms of the agreement, Merck & Co., through a subsidiary, will acquire all outstanding shares of Eyebio for up to $3 billion, including an upfront payment of $1.3 billion in cash and a further potential $1.7 billion in developmental, regulatory, and commercial milestone payments.

The closing of the proposed transaction will be subject to certain conditions, including the expiration of the waiting period under the Hart-Scott-Rodino Antitrust Improvements Act and other customary conditions. The transaction is expected to close in the third quarter of 2024.

EyeBio is developing a pipeline of clinical- and preclinical-stage candidates for the prevention and treatment of vision loss associated with retinal vascular leakage, a known risk factor for retinal disease.

Jeito first invested in EyeBio in February 2022, just 1 year after its creation, as co-lead investor of a $65 million series A funding. In November 2023, Jeito participated again in EyeBio's $65-million extension of its series A financing, in line with Jeito's refinancing strategy to support portfolio companies with a significant deployment of capital at every value milestone reached. These financing rounds were made alongside other major investors in the life sciences industry: SV Health Investors, Samsara BioCapital, MRL Ventures, Bain Capital Life Sciences, Omega Funds and Vertex Ventures HC.

As a leading investor, Jeito fruitfully collaborated with EyeBio's outstanding management team and has been a driving force in the strategic development of the company that led to faster development timelines. With the steady strategic, operational and financial support of Jeito, EyeBio's talented and experienced management team, highly recognised for their strong track record of developing ground-breaking ophthalmology therapies, has been able to design and execute an ambitious development plan, establishing in fast timeline the Proof-of-concept of Restoret in two indications: diabetic macular edema (DME) and neovascular age-related macular degeneration (nvAMD).

In June 2023, EyeBio launched Phase 1b/2a AMARONE (Anti-permeability Mechanism and Age-Related Ocular Neovascularization Evaluation) study, its first clinical trial of its lead asset Restoret, a Wnt agonist, in two retinal diseases with first positive results reported in February 2024, as patients treated with Restoret experienced visual, anatomic, and safety positive outcomes. Restoret is anticipated to advance into a pivotal Phase 2b/3 trial for the treatment of patients with (DME) in the second half of 2024.

EyeBio's acquisition for up to $3 billion, which comes 1 week after the acquisition of another portfolio company (HI-Bio by Biogen Inc. (Nasdaq: BIIB) in autoimmune diseases for up to $1.8 billion) demonstrates Jeito's unique and differentiated investment model. Jeito selectively invests in high-quality and cutting-edge assets in severe diseases that meet the strong Pharma demand for breakthrough innovations and brings its integrated and extensive range of expertise provided by its multitalented team to companies in order to accelerate innovation and deliver value.

Jeito Capital is a global leading private equity fund with a patient benefit driven approach that finances and accelerates the development and growth of ground-breaking medical innovation. Jeito empowers and supports managers through its expert, integrated, multi-talented team and through the investment of significant capital to ensure the growth of companies, building market leaders in their respective therapeutic areas with accelerated patients' access globally, especially in Europe and the United States. Jeito Capital has €534 million under management and a rapidly growing portfolio of investments.

CARGO Therapeutics Announces $110-Million Private Placement Equity Financing

CARGO Therapeutics, Inc. recently announced it has entered into a securities purchase agreement for a private investment in public equity financing that is expected to result in gross proceeds of approximately $110 million, before deducting placement agent fees and other expenses.

The private placement included participation from both new and existing investors including EcoR1 Capital, Woodline Partners LP, Saturn V Capital, Opaleye Management, funds and accounts advised by T. Rowe Price Associates, Inc., Novo Holdings A/S, Perceptive Advisors, RTW Investments, LP, Samsara BioCapital, Wellington Management, Ally Bridge Group, Third Rock Ventures, and a large investment manager.

In the private placement, CARGO is selling 6,471,000 shares of its common stock, at a price of $17.00 per share. The private placement is expected to close on May 30, 2024, subject to the satisfaction of customary closing conditions. The private placement is being conducted in accordance with applicable Nasdaq rules and was priced to satisfy the "Minimum Price" requirement (as defined in the Nasdaq rules).

"We are pleased with the strong support we've received from leading healthcare investors, which we believe is a testament to their conviction in our team, our ability to execute, and importantly our mission to bring potentially curative cell-therapies to cancer patients with high unmet needs," said Gina Chapman, President and Chief Executive Officer. "As we continue to make great progress on our potentially pivotal Phase 2 study of firi-cel in LBCL patients who have R/R from CD19 CAR T therapy, this financing will be key in supporting BLA preparations in addition to advancing our CRG-023 program, which is a novel tri-specific CAR T designed to overcome multiple mechanisms of resistance."

Jefferies, TD Cowen and Piper Sandler are acting as joint placement agents for the private placement.

The securities being issued and sold in this private placement have not been registered under the Securities Act of 1933, as amended, or applicable state securities laws, and may not be offered or sold in the United States except pursuant to an effective registration statement or an applicable exemption from the registration requirements. CARGO Therapeutics has agreed to file a registration statement with the Securities and Exchange Commission registering the resale of the shares of common stock issued in the private placement.

GlycoNex & PrecisemAb Sign Technology Licensing Agreement to Advance Development of Novel Anti-Glycan Antibodies for Cancer Therapy

GlycoNex (4168, hereinafter referred to as GNX) and PrecisemAb recently announced a technology licensing agreement to develop a new generation of an anti-glycan antibody drugs aimed at increasing antibody specificity, reducing drug side effects, and enhancing treatment outcomes for a variety of solid tumors.

Under the agreement, GlycoNex will license PrecisemAb's Universal Antibody Lock (UAL) technology platform, which modifies antibodies to inhibit their activity until activated by tumor proteases. Deploying UAL in conjunction with GlycoNex's anti-glycan antibody platform offers the potential to improve antibody drug behavior by enabling precise therapeutic effects on tumors, while enhancing the safety and tolerability of such drugs by reducing side effects caused by on-target, off-site binding.

"We are excited to collaborate with PrecisemAb and integrate the company's Universal Antibody Lock technology into our platform for developing anti-glycan antibodies targeting cancer-related glycoproteins," said Dr. Mei-Chun Yang, CEO of GlycoNex. "Our goal is to develop drugs capable of selectively activating in the tumor microenvironment, precisely targeting and killing tumor cells, while remaining inactive in the circulatory system and normal tissues, thereby reducing drug side effects and improving patient quality of life."

Dr. Yun-Chu Lu, Chairman of PrecisemAb, added "It is an honor to collaborate with Taiwan's leading glyco-biotech company, GlycoNex, in the development of innovative cancer treatments with anti-glycan antibodies. By applying PrecisemAb's Universal Antibody Lock technology, we aim to develop anti-glycan antibodies that offer patients safer treatment options."

The Universal Antibody Lock technology was invented by Professor Tain-Lu Cheng's team at Kaohsiung Medical University and exclusively licensed to PrecisemAb. This technology can be widely applied in the fields of monoclonal antibody drugs, antibody-drug conjugates (ADCs), and bispecific antibodies, with a production process similar to that of conventional antibodies. The UAL platform is protected by patents in 18 countries.

GlycoNex has 20 years of expertise in researching tumor-specific glycans and developing cancer-targeting antibody drugs. The Company is currently conducting international clinical trials for its own new drugs and biosimilars, including its lead program, GNX-102, which targets tumor-associated glycans and has demonstrated promising results in clinical trials to date.

GlycoNex Inc. is a clinical-stage biotechnology company focused on the development of glycan-directed cancer immunotherapies that effectively inhibit tumor growth while minimizing side effects. GlycoNex possesses a robust pipeline led by GNX102, a humanized monoclonal antibody (mAB) designed to target abnormal sugar molecules in cancer cells. GNX-102 has successfully completed Phase 1 clinical trials with data demonstrating excellent safety and promising efficacy. GlycoNex is also advancing a portfolio of antibody-drug conjugates (ADCs) that precisely attack cancer cells while sparing healthy tissue. GlycoNex is headquartered in New Taipei City, Taiwan.

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Formulation Forum

Advances in Drug Delivery by Antibody Drug Conjugates (ADCs)

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

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INTRODUCTION

With the launch of the very first Antibody Drug Candidate-based drug Mylotarg™ in 2020 for treatment of acute myeloid leukemia (AML), antibody drug conjugates (ADCs) have revolutionized the drug industry over several decades. Out of more than 267 clinical trials, 12 drugs have been approved by the FDA (Figure 1).[1]

FIGURE 1

ADC drugs approved shown by blue arrows and withdrawn by red arrows.

ADCs bring a new and innovative approach to target diseases, especially in the delivery of cancer drugs in a safe way. While conventional chemotherapy treatments remain widely used, ADC technology requires additional steps for the delivery of chemotherapy agents or payloads via a linker attached to a monoclonal antibody that specifically binds to a specific target expressed on cancer cells, thus sparing healthy cells from damage. Thus, ADCs are targeted medicines that deliver chemotherapy agents directly to cancer cells. After binding to the target protein or receptor at the cell surface, the ADC releases a cytotoxic drug into the cancer cells. These drugs can be encapsulated in lipid nanoparticles (LNPs) or directly tethered through linkers to antibodies.

Human monoclonal antibodies (IgG), a heterodimer protein (IgG) composed of two distinct fragments, the antigen binding fragment arms (Fab) and fragment crystallizable stem (Fc), are engineered to carry human antibody genes and act as an ideal delivery platform for ADCs. Highly cell-specific with long circulating half-life then offer minimal immunogenicity. As shown in Figure 2A tethered with chemical "linkers" as one entity, these antibodies and cytotoxic drugs are less prone to cleavage, thus making them very stable. As the drug penetrates into the tumors, these cells die by damaging their DNA or by preventing new cancer cells from forming and spreading.[2] In Figure 2B, the LNP carrying the payload is attached with specific site of antibody via a ligand.

FIGURE 2

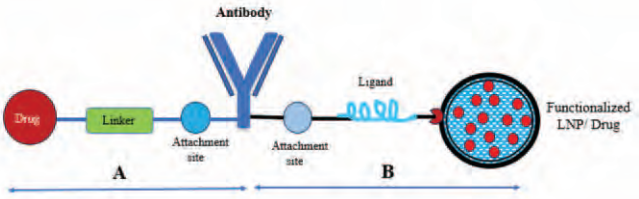


Illustration of an antibody carrying drug attached via linker (A) and drug encapsulated LNP attached with antibody via ligand (B).

The following will focus on two aspects of drug delivery through ADCs. One, where an antibody is conjugated via a ligand with functionalized LNPs carrying cytotoxic drugs; and two, where an antibody is conjugated directly with drug through a linker at the specific site. Let's consider the latter one first as several ADCs have been approved in the recent past.

ADCS: UNDERSTANDING THE MECHANISMS

ADC delivery requires three basic necessary steps. First, an antibody binds with target antigen on the surface. Second, antigen-ADC complex is then internalized into target cell by receptor mediator endocytosis. And third, cytotoxic drug is released by lysosomal enzymes, which trigger cell death. ADC clinical activities are modulated by various factors, namely, target antigen, conjugation chemistries, linker attributes, payload potency, and tumor models.

Key Components

Target antigen – For an ADC to be completely internalized though endocytosis, the antigen density should be 10,000 copies/cell or higher. It is important for delivery of the payload to target the cell to avoid any subsequent cytotoxicity.[3] In other words, overexpression of antigen at the tumor surface compared to normal cells is critical for minimizing the drug cytotoxicity and maximizing the efficacy of drug. For example, overexpression of HER2/neu antigen at the tumor tissues compared to healthy tissues leads to robust and efficient internalization of payload into HER2-target cells. Others with a lesser degree of antigen target expression on cell surface can lead to failed clinical trials when tested at biological doses, and termination of the investigation.[4]

ANTIBODY

It is a biological targeting epitope that promotes the internalization of drug through a receptor-mediated mechanism. It is highly effective as ADC biologics with respect to mere biologics' affinity. With the antigens overexpressed on cell surface, ADC biologics could help mitigate on target/off toxicity on normal cells but can retain potency against tumor cells, suggesting further safety and higher efficacy of antibody-directed drugs. For instance, in a preclinical study, ADC RN765C demonstrated the killing of EGFR receptor mediated tumor cell lines while minimizing the toxicity against normal human cells.[5]

CONJUGATION & LINKER

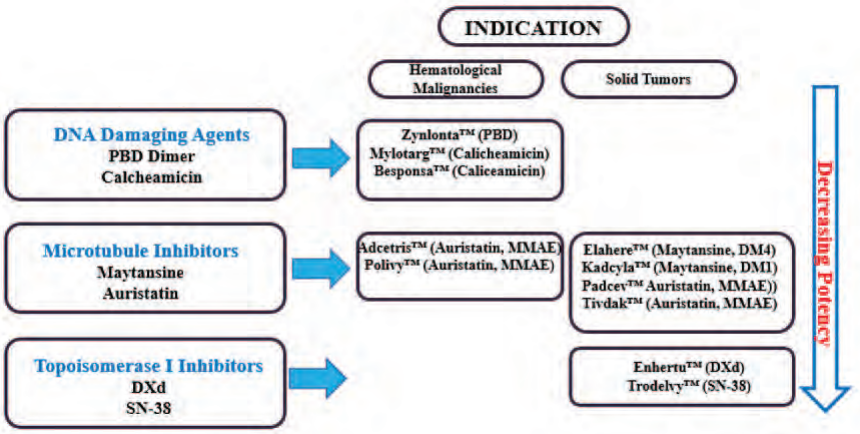
Lysine (amino group) and cysteine (sulfhydryl group) are non-specific amino acids of antibodies for biologic conjugation. The amino acids moieties create more homogeneous ADC drug products with greater safety profiles and improved pharmacokinetic properties. Of the 267 clinical ADCs, 111 candidates utilized non-specific amino acids conjugation, 72 candidates utilized site specific conjugation.[1]

Linkers are cleavable or non-cleavable. The cleavable linkers are designed to be unstable and deliver the payload inside the cell by hydrolysis or proteolysis, or thiol reduction among other mechanisms. Unexpected extracellular cleavage could lead to adverse effects or increased efficacy by being recognized by a tumor antigen- expressing cell leading to diffusion through plasma membrane. In non-cleavable linkers, like the approved ADC drug Kadcyla, the payload is released following proteolysis by lysosomal enzymes leading to release of modified payload-adduct that inhibits the diffusion across the plasma membranes and results in lowering of systemic toxicity and efficacy of drug. In ADC drugs like Enhertu that employs a cleavable linker, it shows much higher clinical activities in tumors with lower HER2 target expression.[6]

DRUG/PAYLOAD

Traditionally, cancer ADC drugs act by three distinct mechanisms. Those include microtubule inhibition, DNA damaging, and topoisomerase inhibition mechanisms. The potency of these payloads could dictate the ADC efficacy and toxicity. Payload ADC effectiveness is dependent upon the number of payload molecules per ADC (drug-antibody ratio, DAR), presence of multi-drug resistance efflux pump, potential untimely cleavage of payload outside cell as by-standard entity, and

FIGURE 3



Approved ADCs classified by mechanism of action, payload, and indication showing in decreasing potency, Zynlonta™ being highest potency and Trodelvy™ being lowest potency. (Pyrrolobenzodiazepines (PBD), IC_{50} 10^{-12} M; Cacheamicin IC_{50} 10^{-10} M) versus doxorubicin IC_{50} 10^{-7} M); Monomethyl auristatin E (MMAE) IC_{50} 10^{-10} M.

TABLE 1

Antibody Drug Conjugate/ Manufacturer	Target	Conjugation	Linker	Drug	Drug-Antibody Ratio (DAR)	Formulation Composition
HEMATOLOGICAL MALIGNANCIES						
Zynlonta™ (lonocastuximab tesirine)/ADC Therapeutics America, Inc.	CD19	Non-specific cysteine	Cleavable, Val-Ala	PBD	2.3	Each 2.2 mL contains 10 mg loncastuximab tesirine-lpyl, 2.8 mg histidine, 4.6 mg histidine.HCl.H2O, 0. 4 mg PS 20, 119.8 mg sucrose in WFI
Mylotarg™ (gemtuzumab ozogamicin)/Pfizer	CD33	Non-specific lysine	Cleavable, AcBut acyl hydrazone disulfide	Calcheamicin	2.3	Each 5 mL vial contains 4.5 mg gemtuzumab ozogamicin, 41 mg dextran 40, 26.1 mg NaCl, 2.7 mg sodium phosphate dibasic, 0. 45 mg sodium phosphate monobasic, 69.8 mg sucrose
Besponsa™ (inotuzumab ozogamicin)/Pfizer	CD22	Non-specific lysine	Cleavable, AcBut acyl hydrazone disulfide	Calcheamicin	2.3	Each 4 mL vial contains 0.9 mg inotuzumab ozogamicin, 0.36 mg PS 80, 2.16 mg NaCl, 180 mg sucrose, 8.64 mg tromethamine in WFI, pH 8
Adcetris™ (brentuximab vedotin)/Seagen, Inc.	CD30	Non-specific cysteine	Cleavable, Val-Cit	MMAE	4	Each mL contains 5 mg brentuximab vedotin 70 mg trehalose, 5.6 mg sodium citrate, 0.21 mg citric acid, 0.20 mg PS 80 in WFI, pH 6.6
Polivy™(polatuzumab vedotin)	CD79b	Non-specific cysteine	Cleavable, Val-Cit	MMAE	3.5	Each 20 mL contains 30 mg polatuzumab vedotin -piiq, 1.8 mg PS-20, 0.82 mg NaOH, 1.77 mg succinic acid, 62 mg sucrose in WFI, pH 5.3
SOLID TUMORS						
Elahere™ (mirvetuximab soravtansine)/ImmunoGen, Inc.	Folate receptor-a	Non-specific lysine	Cleavable, Sulfo-PSDB	DM4	3.4	Each mL contains 5 mg of mirvetuximab soravtansine-gynx, 0.22 mg glacial AcOH, 0.1 mg PS 20, 0.53 mg sodium acetate, 90 mg sucrose in WFI, pH ~ 5.0
Kadcyla™ (trastuzumab emtansine)/Genentech, Inc.	HER2	Non-specific lysine	Non-cleavable SMCC	DM1	3.5	Each mL vial contains 20 mg adotrastuzumab emtansine, 0.02%, PS 20, 10 mM sodium succinate, 6% sucrose, pH of 5.0
Padcev™ (enfortumab vedotin)/Seagen, Inc.	Nectin-4	Non-specific cysteine	Cleavable, Val-Cit	MMAE	4	Each mL contains 10 mg enfortumab vedotin-ejfv, 1.4 mg histidine, 2.31 mg histidine.H2O, 0.2 mg PS 20, 55 mg and trehalose, pH 6.0
Tivdak™ (tisotumab vedotin)/Seagen Inc.	Tissue factor	Non-specific cysteine	Cleavable, Val-Cit	MMAE	4	Each mL contains 10 mg tisotumab vedotin-tftv, 30 mg mannitol, 2.11 mg histidine, 3.44 mg histidine. HCl, 30 mg sucrose, pH 6.0
Enhertu™ (trastuzumab deruxtecan)/Daiichi Sankyo Inc.	HER2	Specific cysteine	Cleavable, GGFG	DXd	8	Each 20 mg/ml vial contains 100 mg fam-trastuzumab deruxtecan-nxki, 4.45 mg histidine, 20.2 mg histidine HCl.H2O, 1.5 mg PS 80, 450 mg sucrose in WFI, pH 5.5
Trodelvy™ (sacituzumab govitecan)/Gilead	Trop-2	Specific cysteine	Cleavable, CLA2	SN-38	7.6	Each vial contains 180 mg sacituzumab govitecan-hziy, 77.3 mg 2-(N-morpho-lino) ethane sulfonic acid, 1.8 mg PS 80 and 154 mg trehalose in 20 mL 0.9% NaCl, pH 6.5

Abbreviations: AcBut- 4-(4-acetylphenoxy) butanoic acid; DM1, mertansine; DM4- ravtansine; Val, valine; Ala, alanine; Cit, citrulline; PBD, pyrrolobenzodiazepine; SMCC, succinimidyl-4-(N-maleimidomethyl cyclohexane)-1-carboxylate; MMAE, monomethyl auristatin E; DX-d, deruxtecan; GGFG, glycine-glycine-phenylalanine-glycine; Solfo-SPDB, (1-(2,5-dioxopyrrolidin-1-yl)-oxo-4-(pyridin-2-yldisulfanyl) butane-2-sulfonic acid).

payload clearance. The net positive versus negative charge and hydrophobicity versus hydrophilicity of payload may influence the clearance rate, which could lead to altering the on-target efficacy and off-target toxicity of an ADC. Metabolism of ADCs can also have impact of safety and efficacy. For example, SN-38, a lactone-based molecule, is inactivated in the liver and can lead to undesired side effects by opening of lactone ring.[7]

Figure 3 shows the approved ADCs classified based on mechanism of action and tumors models.

The FDA has approved thus far 11 ADCs for hematologic and solid tumors as shown in Figure 2. Among them, Mylotarg™, approved in 2010 and withdrawn for safety concerns, was re-approved in 2017 at a much lower dose in combination with chemotherapy. Blenrep™, launched in 2020, was withdrawn in 2022 due to lack of post approval clinical data (Figure 1). Among 11 approved ADCs, 6 utilize microtubule inhibitor mechanism, 2 topoisomerase inhibition mechanism, and 3 ADCs involved with DNA damaging mechanism. These drugs or payloads with the highest potency are DNA damaging agent PBD (IC_{50} in picomolar range to lowest potency topoisomerase I inhibitor SN-38 with an IC_{50} values in nanomolar range.[8]

Table 1 shows the ADC approved drugs by indications and with other details.[1]

LNP-ADCs FOR DELIVERY OF ANTICANCER DRUGS

As noted in Table 1, all ADCs that are administered as a solution form have been approved for selective and targeted delivery of cancer drugs to achieve desired efficacy at lower loses and minimize the adverse effects.

TABLE 2

Lipid Nanoparticles	Lipids	Drug	Ligand	Coupling Method	Cancer Cell/In Vitro
Saturated Lipid Nanoparticles (SLNs)	DSPE-PEG2000-COOH, stearic acid, cacao butter	Doxorubicin	EGFR mAb	Carbodiimde	U-87 MG (glioblastoma)
	DOPE, cholesteryl oleate, triolein, Cholesterol, DC-Cholesterol	Paclitaxel	Cetuximab Trastuzumab	Maleimide	NCI-H1975, NCI-H1650, (jn vitro) lung and breast (in vivo)
Nanostructured Lipid Carriers (NLCs)	DSPE-PEG-NH_2, stearic acid, glyceryl monostearate, MCT	Docetaxel	Flk-1(A-3) mAb	BS3 crosslinker	HepG2 (HCC), A549 (lung), B16 (melanoma)
	DSPE-PEG-maleimide, oleic acid, Compritol 888 ATO, Soy-PC	Paclitaxel 5-Dimethylnobiletin	Cetuximab	Maleimide	A549 (lung cancer)
	Glyceryl monostearate, Soy oil	Irinotecan prodrug Qercetin	Conatumumab	Carbodiimide	HT-29 (colon)
	DSPE-PEG2000-maleimide, Caprylic/capric triglyceride, PEG-40 hydrogenated castor oil	Docetaxel	Bevacizumab	Maleimide	U-87 MG A172 (glioblastoma)
Liposomes	DSPE-PEG-COOH, soy lipid, Cholesteraol, DOPE, cholesteryl hemisuccinate	Docetaxel	VEGF mAb	Carbodiimide	MCF 7 (breast)
	DSPE-PEG2000-maleimide, HSPC, cholesterol, DSPE-PEG2000	Afatinib	Cetuximab	Maleimide	A547 H1975 (NSCLC)
	DSPE-PEG2000-maleimide, HSPC, cholesterol, DSPE-PEG2000	Doxorubicin	PD-L1 mAb	Maleimide	B16-OVA (Melanoma)
	DPPC, cholesterol, DSPE-PEG2000-maleimide, DSPE-PEG2000	Paclitaxel	Ab Fragment	Maleimide	BxPC3 (Pancreatic)

LNP-ADCs have gained ground in the recent past for selective and efficient delivery of cancer drugs.[9] As shown in Figure 1, these LNP carriers require surface functionalization with their carboxyl groups to tether antibodies via known chemical reactions requiring 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) and N-hydroxy succinimide (NHS) couplings with primary amines of antibodies. Other preferred reaction is via site-specific free sulfhydryl groups, created by antibody reduction or thiolation in the Fc region, which can be conjugated to maleimide-activated amino groups of the LNPs. Functionalization through covalent conjugation of antibody results in stable bond formation and allows for controls of ligand density. Considering the hydrodynamic radius of antibody (20 nm), the size of chemically functionalized/conjugated LNPs is expected to increase by 40 nm. The smaller size of antibody clearly allows deeper penetration into tumor cells.

LNPs can be activated by two different methods. First, it can be engineered together with lipid and targeting ligands, and second, a targeting ligand can be post inserted into LNPs. The latter is preferred because the ligands are better exposed at the outer surface LNPs as opposed to encapsulating the ligand within the LNPs in the previous case, allowing lesser degree of exposure to the outer surface. Typically, LNPs are designed with aims to long circulating DSPE-PEG bearing different functional groups such as amino (DSPE-PEG-NH_2), carboxyl (DSPE-PEG-COOH), maleimide (DSPE-PEG-maleimide) or NHS (e.g. DSPE-PEG-NHS), followed by modification with antibody.

Table 2 shows a number of LNPs-antibody conjugates investigated in the clinical studies, but none have yet approved as drug products.

In addition to LNPs, polymer-based PLGA-based NPs have also been investigated for delivery of drugs via ADCs. For example, Hu, et al tested the paclitaxel carrying PLGA conjugated antibody against the carcinoembryonic antigen overexpressed in 90% pancreatic tumors and observed complete internalization in BxPC-3 pancreatic cells with excellent cytotoxicity activities as opposed to non-targeted drug.[20] Wei, et al also delivered effectively the PLGA-salinomycin through anti-CD44 Fab's antibody ligand to suppress the prostrate cancer cells.[21]

FUTURE PERSPECTIVE & SUMMARY

As we continue to address the modern and yet more complicated challenges in drug development for formulation of innovative small molecules and large molecules to find cures for life-threatening diseases, the precise delivery of drugs to target cells is critical for preventing adverse effects and improving efficacy of drugs. Thus, finding the appropriate technology to deliver ADCs is challenging and remains at the forefront of the industry. To date, only 11 drugs have been approved as ADCs, primarily formulated in "aqueous solutions" containing ingredients or excipients approved in injectable drug products and are also listed in the FDA's inactive ingredient database.

In the recent past, attempts have been made for conjugating antibodies with polymeric and lipid nanoparticles (LNPs) as carriers for oncology drugs, but no drugs have been approved yet. In spite of the challenges, the innovation continues as more drugs enter clinical trials.[22,23] The future looks brighter than ever before. It is because the functionalized LNPs can be ideal for conjugation with antibodies (Figure 1) and be used as state-of-the-art drug delivery systems for targeting specific tumor cells to improve therapeutic efficacy by selectively binding of antibodies to receptors overexpressed in angiogenic endothelial cells or cancer cells.[9] Ascendia's capabilities in LipidSol®, a lipid-based technology, can be engineered to fit with ADCs for targeted delivery of potent drugs to tumor cells.[24] ◆

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AMORPHOUS SOLID DISPERSION SPECIATION

Impact of Polymer Chemistry & Drug Properties

By: Wesley K. Tatum, PhD

INTRODUCTION

Amorphous solid dispersions (ASDs) are the most successful formulation technology for oral delivery of poorly soluble compounds. ASDs, usually formed by spray drying, convert a crystalline form of a drug to an amorphous state. The amorphous state is a high-energy physical form that can enhance solubility beyond that of crystalline forms. In an ASD, API is typically formulated with a polymer that helps to both maintain the API in the amorphous form in the solid state and may act as a precipitation inhibitor to sustain the amorphous solubility upon dissolution.

Additionally, the congruent dissolution of API and polymer in the ASD particle can lead to the generation of solubilized drug-polymer colloids.[1] Drug-polymer colloids can further enhance oral bioavailability by increasing the rate of diffusion of API, relative to undissolved solids, through the unstirred boundary layer to the surface of the intestinal epithelium. This can result in a rapid resupply of dissolved drug as API permeates through the epithelium.[2]

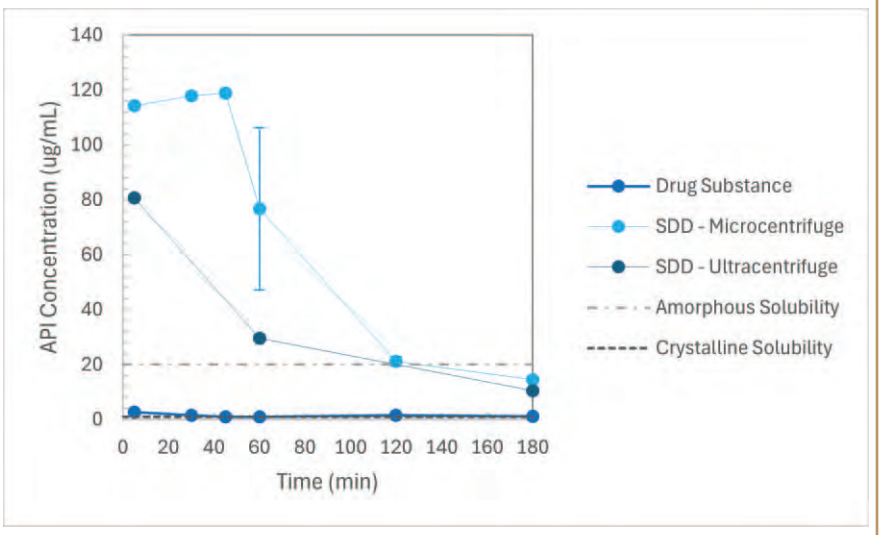
Formulation development of ASDs focuses on polymer selection, the ratio of drug to polymer, and the design of the ASD particles to develop a system that is physically stable while also demonstrating optimal performance. ASD performance is defined by enhancement in bioavailability, driven by supersaturation of dissolved drug and the formation of drug-polymer colloids. The following focuses on the use of *in vitro* techniques for characterizing ASD performance and on how these techniques can be used to help better understand the role of polymer chemistry in ASD performance.

BIORELEVANT DISSOLUTION STUDIES

The biorelevant dissolution study aims to evaluate the behavior of an API, drug product intermediate, or drug product under biorelevant conditions. Biorelevant conditions in these studies are defined primarily by the media composition and API concentration. The two most typical variations of this test are the "one-stage" and "two-stage" tests, referring to evaluation in simulated intestinal fluid or in simulated gastric fluid followed by a dilution into simulated intestinal fluid, respectively. These studies are often referred to as "non-sink" dissolution studies for low solubility compounds, as the target doses *in vivo* are typically well above the solubility of API in biorelevant media. For amorphous formulations, these studies are well-suited for assessing the potential for solubility enhancement relative to the crystalline API. Typical time courses may be from 3-24 hours and allow for assessment of the transient solubility enhancement that is typical of many amorphous systems.

A common dissolution procedure involves removing a sample from the dissolution vessel, centrifuging this sample using a microcentrifuge, and subsequently determining the concentration of drug in the supernatant. The material removed during centrifuging consists mostly of undissolved material suspended in the dissolution media. Simple measurements of the supernatant in the saturated, "non-sink", solutions obtained in these studies quantitates the apparent solubility of the enabled formulation. This apparent solubility comprises dissolved drug, drug in bile-salt micelles (if included in the biorelevant media), and drug in drug-polymer colloids.[3] These drug-containing "species" are useful when comparing formulations. However, additional insight into the speciation can be powerful toward understanding the performance of these formulations. For example, ultracentrifuga-

FIGURE 1



Biorelevant Dissolution "Spring & Parachute" behavior of an ASD. Microcentrifuged samples contain free drug, drug in micelles, and drug-polymer colloids. Drug-polymer colloids are typically removed through ultracentrifugation. The drug substance data corresponds to dosing of crystalline drug alone.

tion can be used to further separate these species. Ultracentrifugation of the supernatant separates the larger and denser drug-polymer colloids from the solvated free drug. The difference in drug concentration in the supernatant after microcentrifugation and ultracentrifugation represents the drug-polymer colloids. Due to the small size and low density of the drug-laden bile salt micelles, ultracentrifugation does not separate these species from freely dissolved (solvated) drug.

Figure 1 illustrates typical results from a single-stage biorelevant dissolution study for an ASD that demonstrates traditional "Spring & Parachute" behavior.[4] In this system, there is an initial supersaturation (the "spring") observed upon dissolution that is significantly above the crystalline solubility. In addition, this concentration of drug typically surpasses the amorphous solubility of the drug. The corresponding ultracentrifuge data demonstrates supersaturation above the crystalline solubility but does not surpass the amorphous solubility. The amorphous solubility is the highest possible solubility the free solubilized drug can achieve in a given media – any apparent solubility measurements that surpass this value are attributable to solubilized species. The difference in the microcentrifuge and ultracentrifuge values thus represents the presence of drug-polymer colloids. Supersaturation is transient, and precipitation to crystalline solubility will eventually occur. The length of time supersaturation is sustained (the "parachute") is determined by the various drug interactions with micelles, polymers, and other excipients and endogenous material *in vivo*.

Figure 2 illustrates results from a single-stage biorelevant dissolution study for an ASD that demonstrates amorphous sustainment rather than the "Spring & Parachute" motif. This behavior, for which the conversion to a crystalline form is exceedingly slow, is common for larger and/or more complex API modalities, such as bifunctional protein degraders and peptides. In this system, the ASD dissolves in an aqueous media to the inherent amorphous solubility, demonstrating significant enhancement over the crystalline API. In many cases, this effect occurs for drug alone, with no excipients, such as polymers, present. However, in most cases, the use of excipients can significantly enhance dissolution rate, and may also provide additional drug species that can transit through the GI tract efficiently. Drug-polymer colloids are evidenced by the difference between the micro- and ultracentrifuged values. However, unlike the "Spring & Parachute" system, the amorphous solubility is sustained within the time frame relevant to this study and to GI transit, and precipitation to crystalline solubility is not observed.

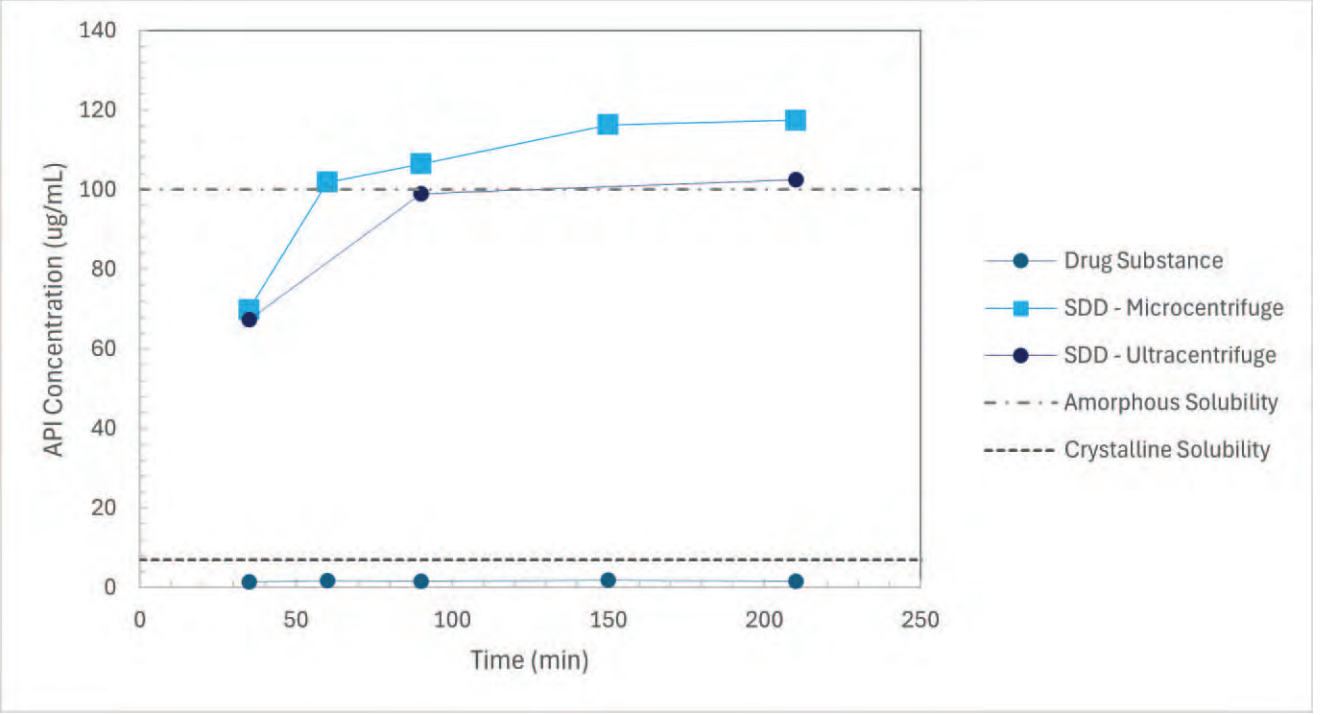
THE EFFECTS OF POLYMER CHEMISTRY

The polymer in an ASD serves several critical functions. In the solid state, the polymer stabilizes the amorphous dispersion by providing a separation of drug molecules and significantly reduced diffusion. A surrogate measurement of diffusion is the glass transition temperature of the dispersion. It is imperative diffusion in the solid state is managed appropriately so the risk of crystallization of the amorphous drug is extremely low. The polymer can also impact powder properties, which may be critical for downstream processing to enable the incorporation of the ASD into an oral solid dosage form. The polymer also impacts performance through the rate of dissolution, acting as a precipitation inhibitor to sustain supersaturation, and by forming drug-polymer colloids that can further enhance oral bioavailability.

Polymer chemistry can impact supersaturation and the propensity for the for-

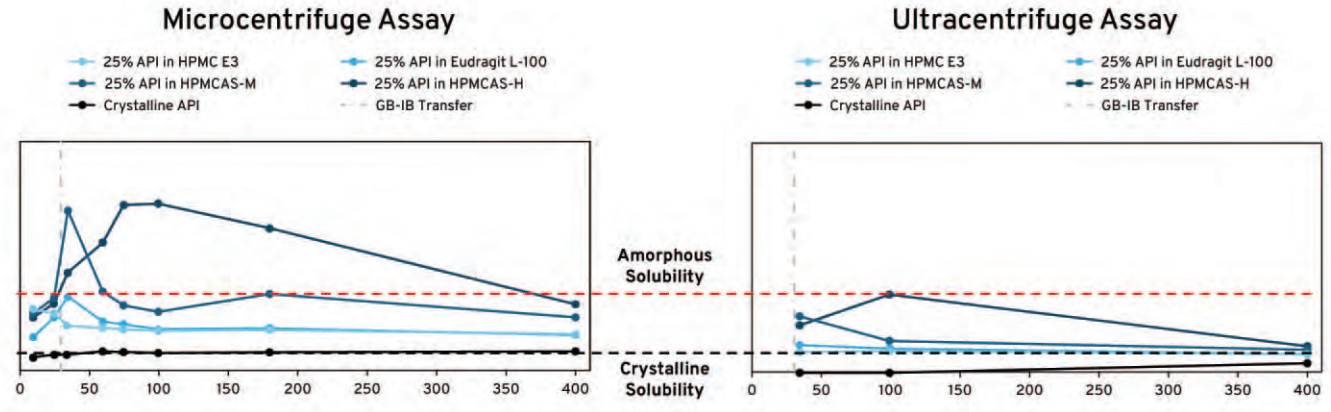
mation of drug-polymer colloids in a variety of ways.[5] In general, the hydrophilicity of a polymer influences the final behavior of an ASD that incorporates the polymer. Typically, more hydrophilic polymers tend to produce polymer colloids that are smaller and less dense, which can aid in initial supersaturation, but can lead to faster precipitation for API that exhibit strong crystallization tendencies. Conversely, more hydrophobic polymers tend to produce larger, more dense colloids that can slowly release drug molecules into solution and can serve to promote sustainment of the amorphous solubility over longer periods of time. However, the effects these differences in colloidal properties have on API solubilization are also influenced by the strength of the interaction between a given API and polymer, as well as their relative dissolution rates and physicochemical properties of the API. Thus, it is important to screen these performance metrics by investigating a range

FIGURE 2



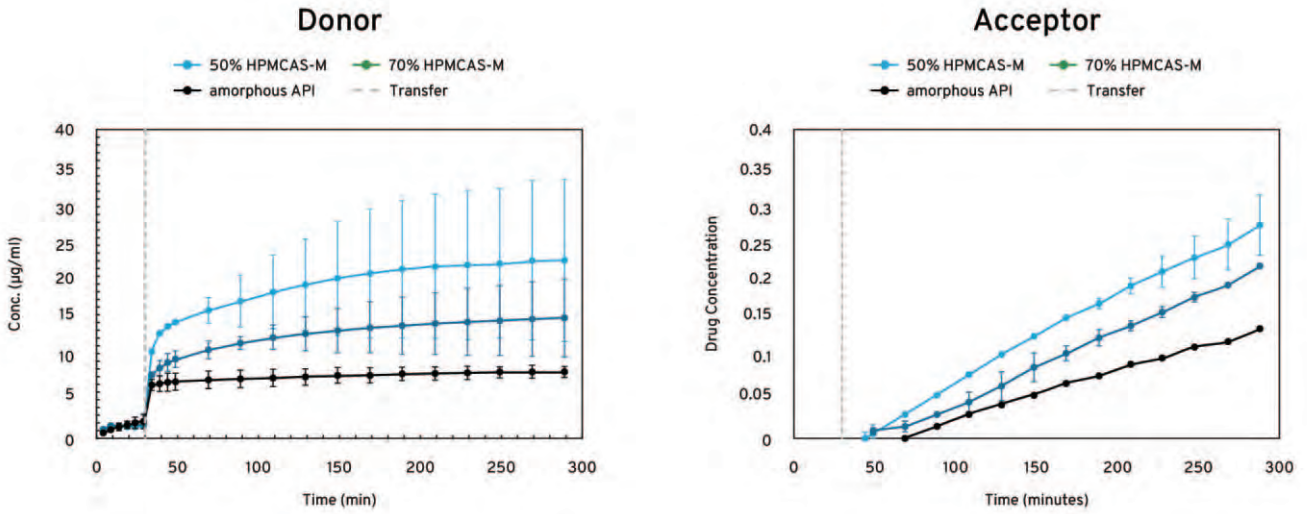
Biorelevant Dissolution behavior of an ASD that sustains amorphous solubility without evidence of precipitation. Micro-centrifuged samples contain free drug, drug in micelles, and drug-polymer colloids. Drug-polymer colloids are typically removed through ultracentrifugation. The drug substance data corresponds to dosing of crystalline drug alone.

FIGURE 3



Two-stage biorelevant dissolution profiles evaluating the effect of polymer chemistry on supersaturation and speciation. Micro-centrifuged samples contain free drug, drug in micelles, and drug-polymer colloids. Drug-polymer colloids are typically removed in the ultra-centrifuged samples.

FIGURE 4



***In vitro* flux testing with a two-stage biorelevant dissolution test performed in the "Donor" chamber (transfer from gastric to intestinal media at 30 minutes). The donor chamber represents the GI-tract, and the acceptor chamber represents the portal vein. The membrane separating the donor and acceptor chamber represents the intestinal epithelium, including the unstirred water lay. Flux between the donor and acceptor chamber represents absorption. Data collected using fiber optic probes.**

of polymers.

Figure 3 illustrates the use of a two-stage biorelevant dissolution study to evaluate the effect of polymer chemistry on supersaturation and the formation of drug-polymer colloids. These experiments demonstrated a clear pattern indicating that enteric or more hydrophobic polymers generally demonstrate the best sustainment profiles, with HPMCAS-H, despite the slower dissolution rate, providing greater sustainment in dissolved drug and the formation of drug-polymer colloids when compared with HPMCAS-M.

FLUX TESTING

While non-sink dissolution experiments are useful for evaluating the extent of solubilization and colloidal speciation for ASD formulations, they do not directly indicate the tendency of those formulations to promote absorption of the drug. To evaluate the ability of the species formed by ASDs to promote permeation across the intestinal epithelium, *in vitro* flux testing can be useful.[6] Flux experiments utilize a semi-permeable membrane that is coated in phospholipids that is placed between two chambers – the donor and receiver chambers. In the donor chamber, a two-stage non-sink dissolution experiment is performed, and the concentration of API is evaluated in both the donor and receiver chamber. By comparing the solubilization and sustainment of the API in the donor chamber, and the extent of diffusion into the receiver chamber, we can assess the general tendency of ASD formulations to promote API permeation *in vivo*.

Figure 4 shows results from an *in vitro* flux experiment that demonstrates the effect of ASD formulation on both supersaturation and permeation. In this experiment, the amount of drug loading in the ASD formulation is indirectly correlated with the extent of supersaturation and permeation, with the 50% HPMCAS-M formulation achieving higher concentrations in both the donor and acceptor chambers. These results indicate this formulation may promote both supersaturation and absorption of the drug.

SUMMARY

With the rise in use of ASDs to enable improved *in vivo* absorption of poorly soluble compounds, it is important to be able to evaluate performance *in vitro* to understand the effect of formulation on *in vivo* performance. The use of non-sink dissolution methods to quantify the apparent solubility of enabled formulations is a valuable approach for selection of the preferred formulations. By leveraging ultracentrifugation to better understand how speciation, influenced by drug behavior and polymer chemistry, enhances supersaturation, additional insights into formulation selection can be achieved. Additionally, *in vitro* flux testing can be useful to understand the ability of enabled

formulations to promote permeation across the intestinal epithelium. A thorough understanding of the application of these methods and a deep understanding of the impact of excipient selection on performance, physical stability, processability, and dosage form performance is critical to optimize the development of ASDs.◆

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BIOGRAPHY

Dr. Wesley Tatum is a Principal Engineer in the Process and Product Development department at Serán. He leads a team of scientists and engineers in characterizing new API and identifying shortcomings for bioavailability. He and his team then screen and select drug product intermediates that address those shortcomings and screen and scale up drug product formulations. During his time at Serán, his work and research has focused on understanding how polymers, excipients, and physiological factors influence speciation, bioavailability, and absorption of drug substances, and amorphous solid dispersions. He earned undergraduate degrees in Physics and Physical Chemistry from Whitworth University and his PhD in Materials Science and Engineering from the University of Washington.

Drug Development
EXECUTIVE

Adi Kaushal

Director & Technology Head, Bioavailability Enhancement

Lonza

Lonza

Lonza: Navigating Today's Challenges in Drug Solubility & Bioavailability

Today, compounds with low solubility or low bioavailability are becoming the rule rather than the norm, as around 90% of preclinical compounds are now estimated to have bioavailability challenges. Low solubility in the earliest stages of drug development presents many challenges for small and emerging biopharma companies. These companies often require the expertise and resources of a strategic partner, like a contract drug manufacturing organization (CDMO), that has the experience, expertise, and advanced technologies to improve dissolution rate, solubility, and overall bioavailability. To help navigate these challenges, CDMOs can leverage approaches like amorphous solid dispersions (ASDs) to enhance drug solubility and bioavailability by converting crystalline drugs to the amorphous form most commonly using spray drying or hot-melt extrusion.

Drug Development & Delivery recently interviewed Adi Kaushal, Director and Technology Head, Bioavailability Enhancement at Lonza, to discuss solubility and bioavailability challenges and Lonza's approach.

Q: Why is there an increasing number of compounds with low solubility or low bioavailability entering today's drug development pipeline? What is the impact on the industry and time it takes to develop these products?

A: For years, poor solubility and low bioavailability have presented drug companies with many challenges in drug development, impacting timelines and ability to scale-up. This is the result of more new chemical entities with complex needs entering drug development pipelines.

Poor solubility often stems from the disconnect between drug discovery and drug delivery. The former often exclusively focuses on receptor binding and activity sometimes at the expense of whether the drug can be delivered to the site of action.

As drug companies face challenges in drug solubility, they are also simultaneously faced with the rising demand for orally administered drugs. Today, patients prefer the convenience, non-invasiveness, and lower cost of oral tablets or capsules. This is because orally administered drugs are much easier to adhere to compared to other approaches for drug administration. Further, these drugs maximize patient compliance and minimize expenses. This is critical, as patient compliance is a paramount priority in drug development. The challenge, however, is the low intrinsic solubility of the API in the gastrointestinal (GI) tract, which results in poor bioavailability.

Q: What techniques do drug manufacturers implement to solve these challenges? What are the benefits?

A: The continued preference for orally administered drugs will present challenges for drug manufacturers to enhance medications with low solubility, which constitute a substantial portion of newly developed chemical entities. To tackle this issue, one effective formulation strategy involves the use of ASDs. These formulations work by increasing drug solubility, thereby facilitating dissolution in GI fluids, and optimizing the quantity of drug that enters the bloodstream. This boost in oral bioavailability holds the potential to enhance patient outcomes by reducing variations in plasma exposure, lowering required dosages, and mitigating potential drug interactions with other medications or food.

While there are several platform technologies and manufacturing techniques to produce ASDs, hot-melt extrusion (HME) is a leading approach based on mature process understanding, small process footprint, continuous operation, and readily scalable. These attributes allow for more flexibility of the unit operation, resulting in relatively lower manufacturing costs and making it a more appealing commercial process train.

HME is also a solvent free unit operation as opposed to spray drying that can not only reduce cost but avoid concerns with solvent impurities and enable sustainability.

Q: Developing a stable ASD formulation can be complex. How do CDMOs approach optimizing the hot-melt extrusion (HME) process for different drug candidates?

A: CDMOs should take a multifaceted approach to optimizing the HME formulation and process for different drug candidates. For example, at Lonza, we conduct thorough pre-formulation studies to gain a deep understanding of a drug's physicochemical properties, including its solubility, melting point, and chemical stability. This helps us identify the most appropriate polymers to achieve bioperformance and physical and chemical stability in the amorphous state.

Next, we optimize the HME process itself. This involves studying various processing parameters such as temperature, screw speed, and feed rate. Our goal is to achieve a uniform dispersion of the drug throughout the polymer matrix while minimizing potential degradation of the drug or polymer.

Finally, we carefully characterize the ASD formulation using advanced analytical techniques. This helps us ensure the drug remains in its amorphous state, is uniformly distributed, and possesses the desired dissolution properties. By following this comprehensive approach, CDMOs can develop stable ASD formulations for a broad range of drug candidates using HME.

Q: What are some current challenges CDMOs face with these techniques?

A: One of the primary bottlenecks is the lack of material-sparing approaches for HME evaluation. This often leads to scenarios where the HME is either not evaluated at all or studied too late when the change of the process can be costly and risky.

Design of a HME formulation and process requires not only a thorough understanding of the API and polymer properties but also requires balancing of bioperformance, API loading, or pill burden concerns as well as chemical and physical stability considerations.

Another area that is often overlooked is the formulation and optimization of the dosage form for HME. While the HME intermediate may demonstrate higher bioavailability, a tablet or capsule (and not the HME by itself) will be the final presentation to a patient. Thus, it is important to formulate a dosage from that not only retains the bioperformance achieved through the HME formulation and process but also minimizes pill burden for a given dose.

Q: When looking for a strategic partner, what criteria should small and emerging biopharma companies look for to help develop their products?

A: It is essential for small and emerging biopharma companies to partner with a CDMO that has an integrated offering to develop their products from clinical stages of development to commercial.

As companies navigate their drug product through development, it is important to focus on the ability to scale that formulation to the next phase. Early clinical trials can require significant quantities of drug product that may be challenging to provide under accelerated timelines without a well-planned scale-up strategy.

ASDs, including those produced by HME, are often more complicated/involved than crystalline API-based products. It is important to work with a CDMO partner that has experience in the ASD products formulating in material sparing way for early stage that can be scaled up when the product enters later phases of development and commercialization.

Further, companies should try to avoid working with multiple outsourcing partners. This can result in duplicated efforts, longer timelines, and increased costs. This can be addressed with a single outsourcing model, where the right partner can perform API synthesis, solid form/salt screening, optimize your formulation, progress your compound through clinical trials, and rapidly scale the drug product to launch.

Q: Looking ahead, what exciting developments do you see in the field of HME and its application in ASD production?

A: One of the key aspects of HME that Lonza has been focused on is making material sparing such that evaluation is possible in early stages when API availability is limited. This enables a parallel evaluation of spray drying and HME, thereby ensuring the most appropriate approach is selected for progression. While the process to achieve ASD is different between solid dispersions (SD) and HME, the material science involved is very similar. Therefore, being able to screen both HME and SD in parallel allows for a direct comparison and selection of the most appropriate path to advance ASD formulation.

Another aspect of further progression in HME across the industry is the expansion of API and polymer space. Currently, the application is limited to APIs below a certain melting point, and the polymer choices are often more constrained than SD.

Finally, the HME process being a continuous unit-op lends itself for integration into a complete process train starting from the API to finished drug product such as a tablet or a capsule. ◆

DEVICE STUDY

Putting Auto-Injector Interchangeability to the Test

By: Alex Fong, MBA

INTRODUCTION

In a crowded market, the right differentiator can hold the key to valuable competitive edge. But that can often be easier said than done when it comes to the pharma industry. Regulatory considerations and the patient experience pose unique challenges when it comes to innovation. The right approach, however, can turn challenges into opportunities that can benefit not just pharma companies but also patients and healthcare systems. The current growth in biosimilars is an example of this in action.

The expiry of many patents for biological medicines is leading to an increase in biosimilars, with developers looking for ways to differentiate their new products from the originator versions.[1] The choice of drug delivery device can be an obvious option to set a pharma company apart from its competitors. But it is not necessarily a straightforward route to success.

At the centre of any decision about which device to choose is the patient. They might be very young or an older person with dexterity issues. And they will almost certainly find it difficult to follow complicated instructions. They are also likely to have become used to whatever device they have been using for their medication in the previous months or years.

All these factors need to be taken into account when deciding whether patients can successfully switch to a different drug delivery device. Because if patients struggle to cope with a new device, there is a risk they will miss out on vital doses of medication – particularly given the trend for self-administration at home without medical supervision.

A STUDY TO ASSESS DEVICE INTERCHANGEABILITY

The best way to discover how patients are likely to cope with a new device is to put it to the test – see how long it takes patients to work out how to use a new device and whether they can successfully carry out test injections. Yet there is a shortage of studies on the ease of switching devices.

To shed light on what happens when patients are asked to switch between two different auto-injectors, Owen Mumford Pharmaceutical Services (OMPS) commissioned an independent study to discover whether regular users of a market-leading three-step auto-injector were able to switch to a new two-step auto-injector and successfully perform injections.

The two devices used in the study were SHL Medical's three-step, button-activated DAI® auto-injector and the two-step, spring-powered Aidaptus® device from OMPS, which uses pressure to activate the injection – instead of pushing a button, the patient just presses the device onto the injection site.

The study involved 52 participants, aged between 16 and 75, who had all been using the DAI auto-injector for at least 3 months. There were 34 women and 18 men, split between the US and the UK. The aim was to test their ability to switch from a familiar auto-injector to a new one – looking at how easily they could learn how to use the new Aidaptus device and whether they could successfully complete injections with it.

The participants had not seen the Aidaptus auto-injector before the study – and they were not given any training, demonstrations, or coaching. They were given the devices in unopened original boxes containing their respective instructions for use (IFU) and asked to administer injections into an injection pad on a table – four injections in total, starting with the DAI auto-injector and then alternating with the Aidaptus. The facilitators were told to intervene only if there was a risk to the participants.

ANALYTICAL MEASURES FOR THE DEVICE INTERCHANGEABILITY STUDY

The primary measure was injection success. An injection was considered successful if the participant correctly delivered the injection into the pad – inserting and using the device as described in the IFU and not removing it until the contents had been fully delivered into the injection pad.

A secondary measure was injection time – calculated from when a participant placed the auto-injector on the injection pad and started the injection process through to when the device was removed from the pad.

Other secondary measures included whether the participant examined the device and how long they took to examine it, whether the participant read the IFU, and their confidence in performing the injections. Demographic factors – age, gender, left or right handedness, and geographical location – and their impact on the other measures were also recorded.

All the secondary measures were calculated by analyzing videos of participants throughout the test process. Ease of use was therefore calculated based on video analysis of the way in which participants handled and examined the device as well as the time taken for injections.

STUDY RESULTS: ASSESSING DEVICE SWITCHING SUCCESS

The study was not intended to be a direct comparison between the DAI and Aidaptus auto-injectors, as all participants were already familiar with the DAI device. The results, however, clearly showed that all participants were able to successfully switch from the three-step auto-injector to the two-step device, with no impact on injection success.

With multiple factors involved in any switch, more user studies are vital for a better understanding of the issues.

Participants used the two devices in a similar way, with injection times (measured as previously described) falling after each injection – indicating familiarization. Mean injection times were similar for both devices. Participants took more time to familiarize themselves with Aidaptus prior to the first injection – compared with the DAI – but this was to be expected, as all participants were already familiar with the DAI.

The injection time across men and women was very similar. However, the men in both countries had a shorter injection time across all Aidaptus injections. Gender, however, did not impact the success of injections and the ability to switch between the two devices. Left or right handedness also appears to have had no impact on injection success – and no significant impact on injection time.

Age also had no impact on injection success. Older users – participants over 40 – typically had longer mean injection times for both the three-step and the two-step auto-injectors, but all injections were successful, irrespective of injection times.

US participants completed their first Aidaptus injection around 30% (4.6 seconds) faster than UK participants – close to their speed when familiar with the devices. This could indicate a greater ability to switch between devices for this US population, but further research would need to be conducted to confirm this.

All participants completed their first injection with Aidaptus successfully, regardless of whether they had read the IFU – which suggests they found both devices easy to use. US participants were more likely to examine the IFU and/or device than UK participants before both Aidaptus injections. Most participants needed to look at the IFU only once. They were able to switch between the two-step and three-step auto-injectors without constantly referring back to the IFU.

DATA GAP ON DEVICE INTERCHANGEABILITY

As the wider availability of biosimilars creates a significantly more competitive market, consideration of the most suitable devices for administering the new drugs is also crucial. That's why pharma companies need access to more data from human factors studies and other ease-of-

use testing – to support regulatory applications for interchangeability determination. The FDA requires a regulatory application to provide evidence that the impact of switching between delivery devices has been assessed.

Ideally, the patient experience should be improved by any switch to a different drug delivery device – at the very least, it should not be adversely affected. With multiple factors involved in any switch, more user studies are vital for a better understanding of the issues. But the OMPS study suggests patients can successfully switch from a three-step auto-injector to a two-step device without external intervention – a valuable step toward de-risking the device choice dilemma.◆

The participants had not seen the Aidaptus auto-injector before the study – and they were not given any training, demonstrations, or coaching.

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BIOGRAPHY

Alex Fong, MBA, is an experienced senior manager in the Insight, Analytics, and Strategy fields. He has applied these skills in a broad range of industries, including the FMCG/CPG, retail, telecoms, and management consulting sectors. He has worked and lived in several international markets throughout his career, including Hong Kong, the US, South Africa, and France.

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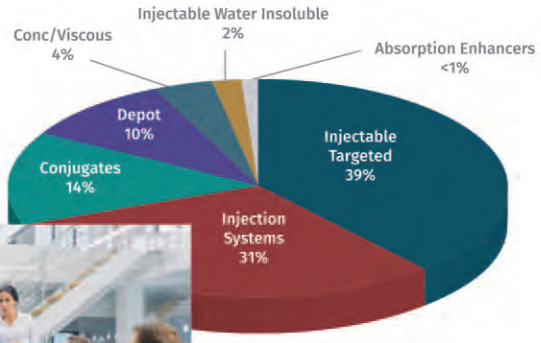

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Special Feature

Outsourcing Formulation Development & Manufacturing: Going Beyond the Science to Become True Partners

By: Cindy H. Dubin, Contributor

Contract Development and Manufacturing Organizations (CDMOs) are critical partners for pharma and biotech companies when it comes to providing innovative solutions that advance the next generations of therapies. To that end, CDMOs are seeking to modify contracts to maintain competitiveness and maximize revenue growth. The top three contract modification priorities are adding more indices, extending contract durations, and ensuring adaptability to shifting market requirements.[1]

Small-molecule specialized CDMOs with expertise in complex formulations, such as (HPAPIs)are growing in importance. The global small-molecule CDMO market will reach almost $85 billion in 2032, up from $45 billion in 2022.[2] While not growing quite as significantly, the global large-molecule CDMO market was valued at $11.6 billion in 2023 and is expected to jump to almost $20 billion in 2029. This market revolves around biologics, monoclonal antibodies, therapeutic proteins, and biosimilars.[3]

Both play a critical part in process development, complex manufacturing processes, and regulatory compliance. "As we continue

Sterile vial filling in Eurofins' closed robotic isolator via filler.

to see the industry evolve post-COVID, 2023 continued to be a difficult year when it came to rising inflation impacting biotech funding and M&A," says Dr. Andrew Lewis, Chief Scientific Officer, Quotient Sciences. "One major takeaway from 2023 was evident: with the best science, it's possible to weather the storm and make truly ground-breaking advancements. We are already seeing turnarounds in 2024, with CDMOs increasingly viewed as strategic partners."

For instance, contractors are providing less off-the-shelf programs, and are instead going deeper to work on the science needed to enable all parts of a program. He says: "The scientific acumen of the outsourcing provider and quality of scientific output can be the deciding factor in a program's success or failure."

In this exclusive, annual report, leading CDMOs speak with *Drug Development & Delivery* about how they are adapting to bio/pharma client needs, their capabilities in handling complex molecules, and how they are transforming from specialist contractors to true partners.

Abzena: A Two-Pronged Approach to Formulation

Abzena offers a customer-centric approach across a range of formulation and manufacturing services that support a biopharmaceutical product throughout its entire lifecycle, from the initial preformulation and generation of a formulation to support toxicology and first-in-human (FIH) clinical trials through to clinical in-use studies, formulation optimization, robustness, and device interaction studies. This enables customers to utilize a single organization for all their formulation and manufacturing requirements, which

Using key technologies, like the Prometheus Panta, Abzena generates critical stability data that aids in the candidate selection process and streamlines formulation development activities.

streamlines and de-risks the process and allows any experience and learnings to be shared across teams, says Gary Watts, PhD, Senior Manager of Analytics at Abzena. This first-hand knowledge of the product can then be applied to rapidly solve any complex problems that may arise downstream.

Broadly speaking, Abzena applies two approaches to formulation studies: First-in-Clinic approach, which is a streamlined methodology focused on enabling the customer to obtain FIH results in the shortest time possible; and a Best-in-Clinic approach, focused on providing a superior product format to the competitors, often applied after Phase 1.

"A practical example of these approaches is where a customer applies the streamlined approach to get to the clinic quickly using a simple formulation at low drug concentration (for intravenous administration), utilizing frozen storage," explains Dr. Watts. "The aim is to ensure there are no adverse events when the drug is administered. The same drug would then be reformulated to provide a 'best-in-clinic' product once known to be safe and efficacious, which could involve concentration of the drug to allow for subcutaneous administration, and optimization of the formulation to maintain a viscosity that is readily injectable, and a product stable to long-term storage at refrigerated temperatures."

He describes how one customer acquired a novel monoclonal antibody (mAb) that was formulated at another CDMO where the approach did not assess the fundamental properties of the mAb. This resulted in phase separation and gelation during refrigerated storage. "These issues were resolved by warming to room temperature (without any apparent impact on quality), however, this was not ideal from a regulatory perspective or for patient administration," Dr. Watts says.

A study was designed to evaluate the fundamental factors crucial to formulation stability and an optimal formulation was identified that showed the desired physical and chemical stability, and was clear, colorless, and free of visible particles after >6 months storage at 2-8°C. In addition, Watts says solubility was sufficiently improved to allow the concentration to be increased to 100mg/mL from 50mg/mL, in line with the customer's requirements.

Over the last couple of years, the proportions of projects based on antibody-

drug conjugates (ADCs), multi-specifics, and vaccines have increased noticeably, making it more important for suppliers to offer customers a streamlined approach to the clinic. "To that end, Abzena's mission is to move new medicines forward to patients faster and we've been investing in our capabilities and forming strategic partnerships to support that," says Dr. Watts.

For example, for the newly launched cell line development platform, AbZelect™, Abzena forged a partnership with ProteoNic Biosciences BV to license their premium protein expression technology, 2G UNic®. This vector technology will significantly improve the production of high-yielding CHO cell lines for Abzena's customers, he says. "By partnering with ProteoNic, we further enhance our existing offering by providing customers with a premium solution that increases the production levels for even the most challenging and complex proteins."

For customers with complex biologics in discovery, the DRIVE-Bio partnership with OncoDesign Services offers an ecosystem of support. Dr. Watts says: "DRIVE-Bio leverages the skills and expertise to develop antibodies in oncology and inflammation through a privileged collaboration that combines Abzena's discovery, development, and manufacturing support of biologics and ADCs with OncoDesign Services' capabilities in optimization to lead selection of naked or pay-loaded preclinical candidates vs target product profile."

Adare Pharma Solutions: Setting Standards in Patient-Centric Solutions

Adare Pharma Solutions is a global technology-driven CDMO providing end-to-end, integrated services, from early-stage development and formulation to commercial-scale manufacturing and packaging. The company has amassed decades of small-molecule expertise focusing on a variety of oral dosage forms including solid dose, capsules, and liquids. The company's technology platforms provide taste masking solutions, customized dose-release profiles, solubility enhancement, and patient-centric dosing solutions. From its seven facilities in the US and Europe, Adare has developed and manufactured more than 65 products that are marketed worldwide.

One customer is a mid-size pharma company with an effective drug product for the treatment of tremors and other persistent, uncontrolled body movements associated with certain neurological conditions. An estimated 5% to 10% of patients with these neurological conditions have dysphagia, which is difficulty swallowing or the inability to swallow.

"Working with the customer, we developed a sprinkle form of the drug that addresses the needs of dysphagic patients," explains Nathan Dormer, Director, Drug Product Development & Site Leader at Adare Pharma Solutions. "These oral granules can be mixed with food or liquid and easily swallowed, improving medication adherence and patient comfort."

Approved by the FDA in April 2024, the sprinkle form is now available in North America, with clinical trials underway for expanded global markets. Dr. Dormer says: "This patient-centric solution highlights Adare's commitment to addressing real-world patient needs, enhancing quality of life, and setting a new industry standard."

Adare is also setting some standards for how it deploys Artificial Intelligence to advance scanning capabilities, giving fresh perspectives on molecules and formulation characteristics. The company is using AI to predict how formulations and molecules will perform in the clinic, guiding partners to focus resources on the most promising candidate formulations and giving the program the highest probability of success in subsequent clinical studies, saving the sponsor time and money.

"Looking to the future, Adare recently reviewed over 25 AI applications and prioritized further focus on those most likely to differentiate our services to clients and speed programs to the clinic, and ultimately to patients," he says.

Adare also embraces ESG principles, driving ethical standards and positive impact across its operations. "With safe and effective solutions, these principles prioritize stakeholder satisfaction, spanning patients, healthcare providers, employees, investors, and communities," says Dr. Dormer. "Our strategy focuses on continuous improvement, setting measurable goals in each ESG pillar to minimize environmental impact, maximize social contribution, and ensure long-term financial resilience."

Almac Pharma Services: Specialized & Flexible for a Range of Formulations

Almac Pharma Services offers a range of formulation, process development, manufacturing, and commercialization capabilities for a variety of oral dosage forms. Through its expert teams, Almac offers product development experience associated with molecule development from candidate selection through to scale up and commercialization. Its range of equipment is aligned to enable batch sizes that are typically required for Phase I clinical phases through to >300kg commercial

Pharmaceutical development at Almac.

batch sizes. Manufacturing capabilities include capsule filling, wet and dry granulation, compression, and film coating. Almac also offers a range of specialized equipment and expertise associated with molecules requiring high containment, bio-enhancement or for specific patient populations such as pediatrics or older patients. Almac designs drug products based on solid fundamental scientific understanding and a consideration of the patients' individual and unique requirements.

Recently, a client required a fixed-dose combination pediatric product. The product contained three active ingredients and the capabilities of the patient to administer the dosage form were a key consideration of the dosage form design. After considering the properties of the drug substance, the dosing regimen, and the patients' needs, a mini-tablet combination product was developed. Mini-tablets of each active ingredient were manufactured, coated, and filled into stick packs at appropriate quantities. The final drug product is then sprinkled onto appropriate food to enable oral administration. The next milestone for this product will be commercialization and ongoing supply.

In addition to pediatric formulations, Almac can handle highly potent molecules. "Our unique capability to handle high potent molecules enables our expert teams to build close partnerships with a number of pharmaceutical and biotech companies," says Terry Ernest, Director, Manufacturing Science and Technology, Almac Pharma Services.

Handling high potent molecules requires complex manufacturing operating processes and procedures, significant engineering controls, and various operational supporting infrastructure. Almac recently invested in this area with new, custom-built facilities being built to expand existing capabilities for handling and processing high potent molecules.

"This specialized manufacturing is best handled by experts providing Almac with the opportunity to build strong partnerships with clients, to enable development and commercialization of their highly potent assets," he says.

Handling a variety of formulations means Almac needs to be flexible in its equipment and facilities to increase capacity. "Providing flexibility to our clients within development discussions as milestones are reached and data is generated ensures that we are approaching projects in an agile way to facilitate adaptations and modifications as projects progress," Mr. Ernest says. "We recognize that planning activities in R&D is not easy, and projects may slow down or accelerate. By communicating regularly with our clients and building trust, we are able to offer maximum flexibility while also maintaining high quality and efficiency within our manufacturing facilities. Within the development process, we aim to scope out experiments with various scenarios in mind so that alternative plans have been pre-discussed and do not delay activities."

ARx: Proprietary Enhancer Promises More Complex Therapies

Leveraging more than 60 years in adhesive and film formulations and manufacturing, ARx specializes in oral thin film and transdermal patch dosage forms. Its expertise in polymers and technology, combined with a proprietary *in silico* preformulation model, allows the company to select the appropriate excipients to meet the targeted pharmacokinetics with a patient-centric design.

"ARx supports partners with specialized capabilities in formulation development, *in vitro* permeation testing, analytical method development, validation, and testing, as well as with clinical, registration, and commercial manufacturing," says Megan Greth, Director of Marketing & BD for ARx. "From a manufacturing standpoint, we have flexible batch sizes of several hundred to millions of finished dose units. As an FDA-ap-

ARx's oral thin film and transdermal patch manufacturing capabilities.

proved manufacturer of several branded and generic prescription drug products, we invested to nearly double our capacity and are a fully integrated partner, delivering serialized cartons and cases."

Customization of formulations and flexibility in partnering are pillars of the ARx partnership model. Each drug substance, as well as its interactions with the body are different, requiring a formulation strategy that starts with the Quality Target Product Profile. In addition, ARx recognizes the business needs of its partners require flexible project plans, batch sizes, timing, and continuous review of risk-based scenarios for progressing development. To reduce risk, production capabilities successfully scale from 3L to 1,000L batch sizes, with the same operating principles, she explains.

When beginning formulation development, ARx leverages proprietary predictive algorithms to streamline and reduce the number of iterations required for selecting the most optimal excipients and enhancers, unique to each API. Ms. Greth says: "This enables us to achieve the targeted results faster and more efficiently; thus, reducing overall time to file new drug products."

ARx recently invented a new formulation and manufacturing technology for oral thin films to solve a delivery issue during formulation development. The client had a unique application that required quick onset of a highly potent active. Delivering micrograms of drug quickly was not achievable with the traditional drug in film matrix technology. Therefore, ARx invented a method to apply the active ingredient to the film surface. This technology was commercially scaled and automated in less than three years from its inception.

"Transdermal patches and oral thin films are specialized dosage forms that have unique abilities to address complex therapeutics by avoiding the first-pass metabolism and, thereby, increasing bioavailability and avoiding adverse events; however, not all molecules easily permeate the mucosal or skin membranes," Ms. Greth explains. "ARx recently discovered a novel enhancer package on a partnered program that allowed for the delivery of a highly prescribed anticoagulant. Without the proprietary enhancer package invented by ARx, the program was not feasible. ARx is excited about utilizing our knowledge in selecting enhancers to allow for more complex therapies to be feasible in the future."

BioDuro-Sundia: Adapting to Meet Client Needs & Schedules

BioDuro-Sundia has been an industry leader in amorphous solid dispersions (SDD and HME) and modified release. This enables development of complex and challenging formulations and processes, along with the traditional solid oral dosages intended for oral administration. In fact, the company recently manufactured a Phase 1 SDD product from formulation development to release testing of the product in three months.

"This makes us one of the few CDMOs that can deliver to client expectations based on technical quality and expertise," says Magdalena Mejillano, Senior Vice President, Clinical Development and Commercial Manufacturing, BioDuro-Sundia. "We are one of the very few CDMOs that can perform pre-clinical to commercial drug product manufacturing in one site. In addition, our site has the permits to handle large amounts of organic solvents for spray drying and coating."

In addition to complex therapeutics, BioDuro-Sundia supports small-volume drugs for rare disease and orphan indications. "We have a wide range of equipment with different capacities that can support these types of products," she says. "We have forged at least three partnerships for commercial drugs using proprietary equipment and technology that will be provided by the client and manufacturing conducted at our facility. These clients will have dedicated suites modified according to their specific requirements."

BioDuro-Sundia will even modify ex-

BioDuro-Sundia specializes in amorphous solid dispersions (SDD & HME) and modified release.

isting suites to enable the installation of client equipment and train staff on their operation. The company has also supported, and continues to support, specialized technologies that are not necessarily in its core competencies by allowing clients to bring in their own specialized equipment and install in customized dedicated suites.

"Our clients' feedback has consistently been about our flexibility in terms of adapting to client needs or meeting a very aggressive schedule," says Dr. Mejillano. "We have two work shifts in manufacturing, but can activate two 10-hour shifts or three 8-hour shifts, if needed. There is also extensive cross-training between formulation and process development staff and manufacturing operators, both clinical and commercial."

Some of the more challenging projects BioDuro-Sundia has conducted that have been resolved and went into successful clinical trial manufacturing include: low solid content, low soluble fast crystallizing API in an SDD formulation (~2-3% solids), optimized process conditions to achieve <7um (D90) particle size of an inhalable product; optimized process and secondary conditions to spray acetic acid solvent mixtures and achieve below-ICH limit residual solvents; and optimized a process to spray (aqueous-based) heat-sensitive biological actives to achieve stable products.

Celanese: Partnering with CDMOs to Enhance Patient Outcomes

According to reports from Fierce Pharma, the pharmaceutical industry is witnessing a remarkable trend: the accelerated growth of CDMOs, which is outpacing the broader market. This surge highlights the critical role CDMOs play in the sector, a dynamic that has been increasingly recognized for its strategic importance.

"At Celanese, our engagement with CDMOs is not merely transactional; it is a deliberate strategic focus to advance our specialized capabilities in material science and drug delivery technologies, particularly in controlled-release applications for biologics," says Tom Quinci, Senior Manager – External Partnerships, Celanese.

Celanese aims to help pharmaceutical companies develop their products by offering the VitalDose® EVA Drug Delivery Platform and formulation expertise for sustained molecule release. "As early research and development efforts scale up into clinical research, we then transfer our initial formulations technology to CDMOs," he explains. "The Celanese internal laboratories and scientists are pivotal in establishing the basic feasibility of these early research efforts. They lay the groundwork for detailed product development, targeting a pharmaceutical company's target product profile. Trusted partnerships and collaborative relationships are essential to this process."

He adds that CDMOs provide comprehensive chemistry, manufacturing, and controls (CMC) services necessary for producing clinical-grade drug products. Partnering with them allows Celanese to efficiently produce and screen for formu-

Celanese scientist testing for drug release.

lations that can be scaled up. This capability ensures that Celanese's innovations are seamlessly transitioned from concept to clinic, ultimately benefiting patients globally.

"Combining Celanese's advanced material polymer and formulation expertise with a CDMO's process development and manufacturing scale-up expertise allows us to work synergistically to achieve success for our mutual pharmaceutical partners," says Mr. Quinci. "This collaboration results in a potent combination where innovation meets execution, providing the industry with high-value, comprehensive solutions particularly vital in the treatment of solid tumors, retinal diseases, and neurological disorders."

As the influence of CDMOs grows within the pharmaceutical industry, so too does the opportunity for strategic partnerships. By aligning Celanese's technological capabilities with the operational excellence of its CDMO partners, he says Celanese is driving innovation and emphasizing a commitment to improving patient outcomes through the value of optimized drug delivery.

Curia: Working Within Tight Formulation Constraints

Curia offers a full range of parenteral formulation development services, as well as clinical and commercial manufacturing of drug product. Formulation development is a critical stage in the drug development process, which involves the optimization of the physical and chemical properties of a drug, including its stability, solubility, and compatibility with different drug delivery systems.

"When envisioning the first-in-human development space, most programs that are brought to our scientists have significant questions yet to be answered, and often times the molecules are new and unique," explains Tyler Jones, Director, Formulation, at Curia. "This provides not only numerous challenges, but also opportunities to develop novel and groundbreaking solutions. A key to success in this ever-changing space is the ability to develop emerging formulations that not only stabilize the molecule but also lead to viable drug products."

These challenges are often related to the molecule itself, but can also be created by the target product profile or route of administration. For example, Curia undertakes projects for intrathecal delivery, which comes with a very controlled formulation space. Being able to work within these tight formulation constraints, while still developing stable and successful formulations, is a necessary skill for success, he says.

As advances in Lipid Nanoparticle (LNP) applications continue to revolutionize the industry, the ability to readily screen and manufacture candidate formulations at phase-appropriate scale is advantageous. "In our experience, we have found that customers often prefer to stay within a technology family (such as microfluidics, jet impingement, T-mixing, etc.) as they progress from early research into clinical drug product supply," says Dr. Jones. "This process continuity through the early development phase streamlines scale-up while protecting material and timeline considerations." Curia's clinical drug product sites have invested heavily into these technologies, offering a full suite of LNP services from bench scale-up to, and including, GMP fill/finish using microfluidics systems.

As therapeutic applications are becoming more complex, CDMOs working in the early development and first-in-human clinical supply area must be flexible, as immediate goals are often changing based on new data, funding, prioritization, and other external forces not under the CDMO's control. "At Curia, we are well-versed in accommodating unique needs and requests to help our partners achieve results," he says. "These requirements range from extremely short timelines to customized experiments looking to answer molecule-specific questions. Building out a knowledge base and making data-driven decisions is the key to successfully advancing programs through the critical early stages of development."

CycloLab Ltd.: Understanding the Nature of Complexation

In the realm of cyclodextrin host-guest complexes, understanding their intricacies is paramount. CycloLab is dedicated to unravelling the mysteries of these complexes using a diverse array of analytical techniques such as nuclear magnetic resonance (NMR) spectroscopy, isothermal titration calorimetry (ITC), phase solubility studies, and capillary electrophoresis (CE).

"NMR stands as a cornerstone in our quest for molecular elucidation," says Dr. Levente Szöcs, R&D director at CycloLab. "By analyzing chemical shifts, coupling constants, and spin-spin interactions, NMR provides invaluable insights into the structure, dynamics, and stoichiometry of cyclodextrin complexes."

To understand the molecular recognition process adequately, determining the stoichiometry of the selector–select and complexation is essential. CycloLab uses the continuous variation method (Job plot) to quantify the stoichiometry of the inclusion complex. "In this experiment, we

maintain the sum of the concentration of the guest and cyclodextrin constant while measuring the 1H NMR chemical shifts (δ) at different guest concentration/CD concentration ratios," he explains.

In most cases, it is 1:1 molar ratio, but CycloLab has examples for 1:2 and 2:1 as well as stoichiometries of higher order. In another set of experiments that resembles a titration, the company can determine the stability constant(s) of the complex.

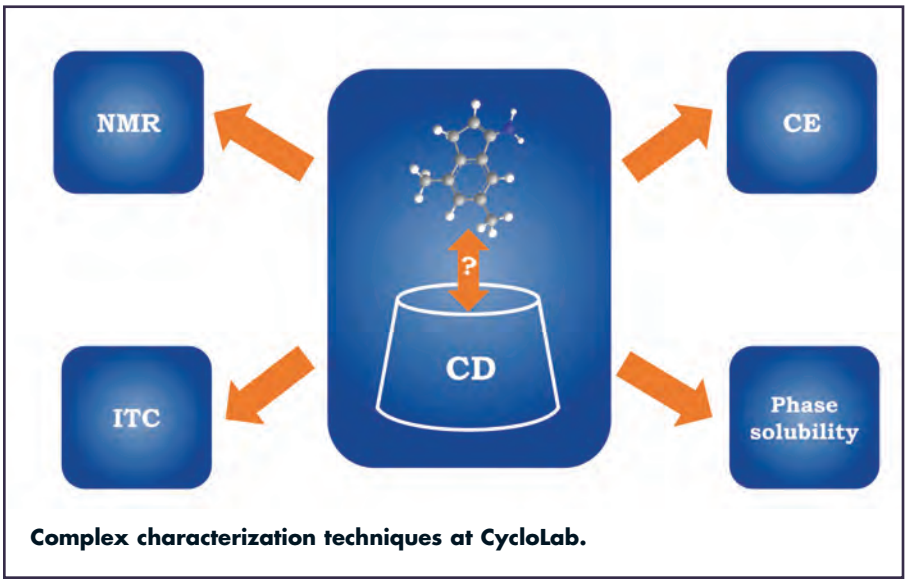
With 2D NMR experiments, like the so-called ROESY, the structure of the complex can be determined. The rationale of these experiments is the nuclear Overhauser effect (NOE), a manifestation of cross relaxation between two non-equivalent nuclear spins that are relatively close (<5Å) in space. Thus, this experiment can confirm inclusion complex formation and also offers insight into the geometry of the complex.

"This spectroscopic study will give detailed information on the weak interactions of host-guest complex formation at the atomic level and unambiguously confirm (or disprove) the formation of an inclusion complex," says Dr. Szöcs.

In the pursuit of understanding binding affinities and thermodynamic parameters, ITC emerges as a powerful tool. Through precise measurements of heat changes upon complex formation, ITC sheds light on the energetics driving cyclodextrin guest binding, offering crucial information for drug formulation and optimization.

Phase solubility studies serve as a cornerstone for quantifying complexation constants and assessing the solubilizing efficacy of cyclodextrins. By plotting solubility profiles against guest concentrations, these studies elucidate the stoichiometry and stability of host-guest complexes, aiding in the selection of optimal cyclodextrin formulations.

Capillary electrophoresis is also a versatile technique for evaluating the interaction strengths between cyclodextrins and guest molecules. Through the separation and quantification of complexes based on electrophoretic mobility, capillary electrophoresis offers valuable insights into complexation kinetics, charge interactions, and chiral selectivity.



Complex characterization techniques at CycloLab.

Eurofins BioPharma Product Testing: Early-Phase Formulation & Sterile Filling

Eurofins BioPharma Product Testing's San Diego site has developed and manufactured a range of drug products from sterile injectables to oral solutions to topical creams. The team is focused on early-phase and small-batch manufacturing, which puts the company in a position to provide the support that challenges large commercial-scale manufacturers.

"Our fully GMP lab has extensive analytical capabilities, enabling our experts to rapidly design and test formulations to arrive at the most stable, clinically-presentable formulations," says Joe Page, PhD, President, Eurofins BioPharma Product Testing San Diego. This spans modalities, including mAbs, mRNA, oligonucleotides, and small molecules.

Additionally, in its BSL2 lab, Eurofins BioPharma Product Testing San Diego has worked with AAV drugs and tissue-derived samples. The company provides GMP sterile fill/finish services (up to 3,000 vials) to advance clients into clinical trials.

"Complex therapies, such as mRNA, mAbs, ADCs, AAV, and oligonucleotides, require an understanding of the critical quality attributes to effectively develop and formulate these modalities," says Dr. Page. For example, excessive antibody aggregation or high levels of mRNA unbound from the LNP could render these treatments ineffective. In addition, these high-value drugs require the greatest level of assurance of sterility that is best achieved by isolator technology in the fill/finish process.

"We have worked with many clients to develop techniques to test these emerging drugs to ensure optimal formulations," he says. "For example, we have tested formulation variants for PS80 levels and tested

the corresponding antibody aggregation levels. These techniques accelerate stability studies conducted on candidate formulations. We collaborate with our sister site in Toronto, Canada, Eurofins Alphora, to source complex APIs, and our Lancaster, PA, site for cell banking, leveraging our network of laboratories to propel our clients' drug journeys. We've also built strong collaborations and relationships with biopharma companies that provide drug substances such as oligonucleotides, mRNA, and DNA."

Eurofins views IT solutions as a key differentiator, which is why the company has continuously developed its software platforms. This allows Eurofins to scale its business, harmonize globally, and customize solutions specific to a client's needs.

As a provider to early-phase clinical clients, flexibility is a critical component to the service. "We understand the need for flexibility and customization and collaborate with our clients during formulation development by recommending excipients and process steps to deliver both a clinically-acceptable, and cost-effective formulation," says Dr. Page.

As formulation development is a strength, one client had an insoluble API that, despite the use of cyclodextrin, still suffered from solubility issues. The Eurofins team worked through the issue and revealed that hold times during the initial dissolution were important to long-term solubility. Dr. Page says: "This seemingly simple, yet critical change enabled this product to move into clinical trials."

Another client's product had solubility and degradation issues. Eurofins discovered that the order of addition was important to minimizing formulation-induced degradation. "We then prepared 12 formulation variants with varying levels of ethanol and polysorbate," he says. "An accelerated stability study resulted in a formulation appropriate for the clinic."

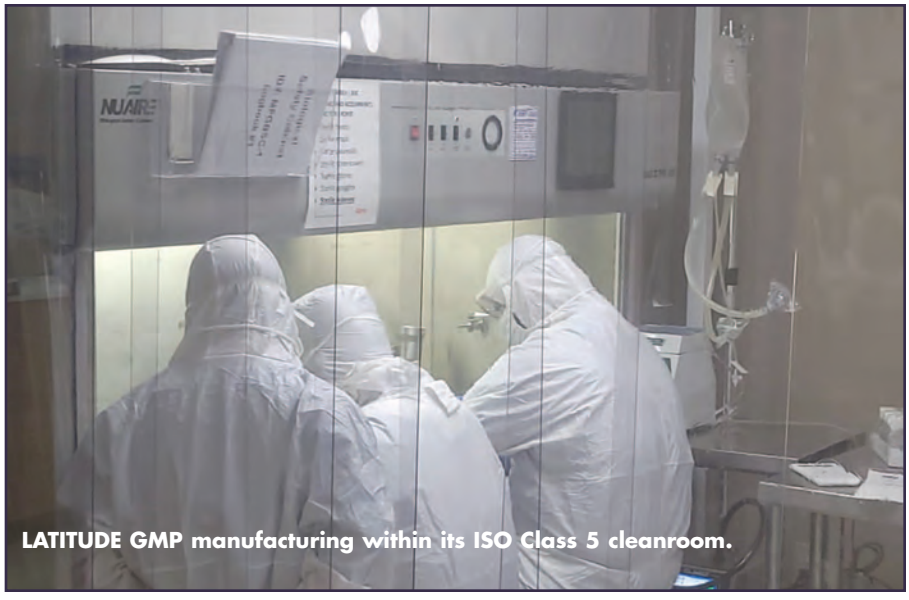
LATITUDE Pharmaceuticals: Flexible & Customized Formulations

LATITUDE Pharmaceuticals is a small California-based CDMO – starting in 2003 as a formulation development CRO – and has strong experience with injectables, oral solids and liquids, ophthalmic, intranasal, and inhalation formulations. Formulation services support clients from preformulation to preclinical and clinical development, including full in-house analytical support and method development. LATITUDE has particular expertise with complex injectable formulations, including nanoparticles, nanoemulsions, and liposomes.

LATITUDE added GMP manufacturing for Phase 1 and Phase 2 clinical trial materials in 2019. GMP capabilities include the manufacture of sterile injectables (vials, bottles, prefilled syringes), oral solids and liquids, and ophthalmics (eyedropper bottles), as well as full method development and validation. Of particular note is a recently added space for GMP aseptic lyophilization to enable even poorly-stable formulations to rapidly enter human clinical trials, says Matthew Singer, Vice President of Business Development. LATITUDE.

LATITUDE prides itself on its flexibility to easily pivot according to clients' changing needs. Clients interact directly with project scientists and each formulation is custom-developed. LATITUDE works with companies of all sizes. One recent client needed to develop an interarticular injection formulation with sustained release of the API. He says that LATITUDE developed a PLGA microsphere-based formulation that provided the PK profile desired by the client, including the necessary analytical methods, and provided the material necessary for animal testing.

In other areas, LATITUDE has worked with numerous clients for oral solid and liquid development, solving issues of solubility and bioavailability with nanoparticles, nanosuspensions, self-emulsifying delivery systems, and LATITUDE's proprietary ClearSol™ solubilization platform.



LATITUDE GMP manufacturing within its ISO Class 5 cleanroom.

Lifecore Biomedical: Handling Process Development & Manufacturing Complexity

Lifecore Biomedical is known for a flexible approach to collaboration, allowing customers to "define the starting line" and be as involved as desired while remaining ready to provide technical expertise. "We offer on-site, person-in-plant camera access for batch manufacturing, as well as remote camera access for clients who can't be on site," describes Alex McDonah, Technical Manager of Business Operations, Lifecore Biomedical. "During all project phases, we welcome face-to-face visits as a key contributor to the establishment and maintenance of close relationships with customers."

From a technical perspective, Lifecore Biomedical has worked with molecules and process fluids across the spectrum of viscosity, pH, light, heat, sterilization sensitivity, and filtration feasibility. Through decades of experience and more than 20 commercial products, the company has developed broad experience and deep knowledge in formulation, filtration, aseptic processing, filling, and finishing. Mr. McDonah says: "We support production processes from simple thaw, filter, and fill/finish to complex formulations with multiple, aseptic processing and formulation steps for solutions that cannot be terminally sterilized or filtered – and everything in between."

An example of complex process development work by Lifecore was recently undertaken for multiple customers requiring the ability to aseptically process materials through homogenization to ascertain specific particle size distribution. In these instances, sterile components were formulated and processed aseptically all the way through to the final drug product.

Supporting projects from simple to complex, Lifecore maintains a responsive approach to unique customer needs.

Lonza: Enhancing Capacity and Technologies to Accelerate Customers' Timelines

Lonza is a global partner to the pharmaceutical and biotech markets with expertise in biologics, small molecules, cell and gene, and capsules and health ingredients. Integrated services and products support from early-phase discovery to custom development and manufacturing of active pharmaceutical ingredients and innovative dosage forms.

To offer customers a more integrated bioconjugates offering, Lonza acquired Synaffix B.V. The acquisition will enable access to Synaffix's payload and site-specific linker technologies. In March 2024, Lonza signed an agreement to acquire Roche's manufacturing facility in Vacaville, CA, which will add significant new capacity to its global network and support the growing global need for large-scale mammalian manufacturing.

"Over the past two years, Lonza has significantly continued to strengthen its development and manufacturing network as well as its technology portfolio to better support customers from the earliest stages of development to market," says Jean-Christophe Hyvert, President, Lonza Biologics.

As is true for most industries today, artificial intelligence (AI), machine learning (ML), and robotics drive the industry forward. Lonza is adopting digital technology


Scientist at Lonza's facility in Visp, Switzerland.

and automation to streamline operations, decrease manual involvement, and improve data-driven decision-making. For example, by leveraging its experience of more than 150 tech transfers, Lonza is investigating the potential of AI and ML applications in product technology transfer.

"Throughout a product lifecycle, manufacturers encounter different scales and different equipment setups during technology transfers," he says. "The number of process variables and critical quality attributes involved in technology transfers add another dimension of complexity. AI and ML applications can be used to predict process performance or critical process steps in such technology transfers, helping to address these complex challenges."

Lonza is also investigating the use of AI and ML in deviation management and change control applications. Such applications can add significant value as transactional intelligence systems. In addition, Big Data, ML, and AI are routinely used in areas such as R&D, computer-aided drug design, protein profile assessment, engineering mammalian expression systems with DNA element design, and in predicting side effects for novel therapy forms.

In downstream processing, spectroscopical methods like Raman are used in combination with an ML algorithm to monitor critical process parameters, allowing production process performance to be monitored without taking a manual sample if an in-line spectrometer probe is installed. Mr. Hyvert says: "This impacts process performance through decreased contamination risk and increased manufacturing speed."

Mikart: Addressing the Demands for Complex Formulations

Mikart offers comprehensive formulation development and manufacturing services for pharmaceutical products, specializing in solid oral and liquid dosage forms and providing end-to-end solutions from development to production. Their focus on quality, flexibility, compliance, and customer service sets them apart in the market. Over the past two years, Mikart has addressed the growing demands for complex therapies in the pharmaceutical industry. The company has focused on expanding its capabilities in both solid oral and liquid oral formulations.

In 2021, Mikart invested in the Korsch XM12 tablet press. This technology enhances the company's ability to develop and produce complex oral solid dose products. It supports the development of fixed-dose combination products and potent compounds, offering advanced compression technology for bi-layer and mini tablets. This acquisition underscores our commitment to meeting client demands for complex formulation development and production of oral solid dose products.

In early 2023, Mikart unveiled a state-of-the-art liquids and suspensions suite. This investment is designed to develop and manufacture robust liquid dosage forms, including complex suspension products and extended-release formulations. The suite is equipped with various temperature-controlled tanks, enabling the handling of a wide range of volumes from 50L to 4,000L, which supports both pediatric and geriatric product development.

Mikart has signed a collaboration agreement with Nano PharmaSolutions, Inc. (NPS) to produce clinical trial materials using the NanoTransformer™ technology. This technology enhances the solubility of pharmaceutical APIs. "By incorporating the NanoTransformer technology, Mikart can address API solubility issues, formulation development, and commercialization of the finished product," says Nazar Elkarim, Vice President of Product Development Services for Mikart. "This unique, solvent-free, nano-granulation process for drug development and manufacturing offers biotech and pharmaceutical companies an alternative solubility enhancement technology and complex therapies."

Dr. Elkarim says that Mikart's goal is to provide value without compromising on quality or service. "We address the need for flexibility by offering customizable solutions to meet the specific needs of pharmaceutical companies and work closely with our partners to develop tailored manufacturing and packaging solutions that

Empowering Pharmaceutical Innovation: Customizable and Cost-Effective Solutions by Mikart.

align with their unique requirements," Gus LaBella, Director of Formulation Development, Mikart, says. "This approach allows biotech and pharma companies greater control over the production process. It ensures that their products are manufactured in an efficient and sustainable way."

Nano PharmaSolutions, Inc.: Single Nanoformulation for All Phases with No Chemical Additives

Poor solubility remains one of the greatest challenges in pharmaceutical development. More than 70% of new chemical entity (NCE) candidates have poor solubility and therefore poor bioavailability, which remains the leading cause for failure of Phase 1 First-in-Human trials. While the number of methods for enhancing drug solubility continues to increase, trade-offs in forms of cost, development time, and formulation bridging animal and PK studies make optimal solutions elusive.

Nanoformulation is an attractive alternative to solid-form solutions like spray drying or hot melt extrusion technologies to enhance solubility and bioavailability. However, nanoformulation is not widely utilized in early drug development of solid oral formulation due to fears of long development time and poor flow characteristics of submicron-size drug particles.

NanoTransformer™ is an easily scalable nanosizing technology that generates drug nanoparticles in the 200-600nm (D50) range. This process uses gentle heat under low pressure to evaporate solid drug substance to gas phase, and subsequently deposit them as drug nanoparticles on the surface of a common hydrophilic granulation excipient (e.g., mannitol, lactose, microcrystalline cellulose). These nano-granules may be used for animal safety studies as aqueous suspensions; for Phase 1 clinical trials as capsules, powder-in-capsule, or powder-in-bottle; and as compressed tablets for later-stage clinical trials – all without changing the base formulation. Using the same nano-granulation for the base oral dosage form in all phases of clinical trials removes the need for bridging PK studies required by regulatory agencies for formulation changes during the development phase. A solvent-free nanoformulation for animal safety studies will ensure the same good exposure of drug is maintained in both animals and humans, says Dr. Kay Olmstead, CEO, Nano PharmaSolutions.

The NanoTransformer granulator is a high-vacuum nano-coater, commonly used in the semiconductor and aerospace industries, enabling the production of nanodrugs under cGMP conditions. "The development time for nanoformulation is rapid and requires very little API, which is suitable for preclinical studies," she says. "Industrial vacuum nano-coaters can generate hundreds of kilograms of nanoparticles; therefore scale-up to production-sized batches is easily achievable."

Nano PharmaSolutions offers GMP manufacturing of clinical supplies of nanomedicines at its co-manufacturing facility at Mikart, LLC. Mikart is a CDMO focusing on developing and manufacturing oral solid and liquid dosage forms. Dr. Nazar Elkarim, Vice President, Drug Development Services, Mikart, says that GMP operation of NanoTransformer technology at Mikart with smooth tech transfer from Nano PharmaSolutions and manufacturing capability for finished dosage forms for various formats (capsules, tablets, pediatric formulations, etc.) provides an easily scalable solution for difficult formulations in all development stages. "This differentiated, solvent-free, nano-granulation process for drug development and manufacturing provides biotech and pharmaceutical companies with an alternative solubility enhancement technology."

Particle Sciences, Inc.: Collaborating to Expand Capabilities to Meet Client Needs

Particle Sciences, Inc. (PSI, an Agno Pharmaceutical company) develops patient-centric complex dosage forms, which include long-acting injectables, implantables, and drug-eluting devices. These dosage forms are developed for challenging APIs, such as water-insoluble, DEA-controlled substances, and highly potent compounds. Examples of form factors include PLGA microspheres, implantable rods, intravaginal rings, and API nano/microparticles. PSI works closely with clients, and in some cases, adds capabilities to support clients' programs, such as commercial aseptic powder filling. Additionally, the company will be building a commercial, aseptic nano-milling line. All capabilities and dosage forms are supported by in-house analytical services (including physicochemical characterization tools), providing a one-stop-shop for clients' target product.

Feasibility programs for drug-eluting devices, nanomilling, and PLGA microspheres are designed to be low-cost, entry screening programs to assess if a clients' API is amenable to one of the stated technologies and to establish some proof-of-concept, explains Onajite Okoh, Director, Drug Device Development for Particle Sciences, Inc., an Agno Pharmaceutical company. "PSI then takes clients into formal development, through cGMP manufacturing and, if it makes sense for both parties,

Particle Sciences Inc. can be a partner for intravaginal ring design.

we may offer them the option of supporting their commercial production. We have partnered with equipment manufacturers to place specialized equipment at PSI to support specific formulation forms, for example, a hot melt extruder to support the development of biodegradable ophthalmic implants. Our parent company, Agno Pharmaceuticals, has added sterile API and excipient commercial manufacturing at the request of our clients."

In addition to meeting client requests, PSI partners with clients to address their needs. "There is a willingness to invest and expand our capabilities to meet the clients' need and timelines," says Shreya Shah, MS, Associate Director, Pharmaceutical Development for PSI. "An example of this is onboarding sterile API commercial manufacturing and sterile powder filling capabilities at the request of one of our clients. We also utilize a phase-appropriate quality approach that has been shown to accelerate our client's development programs, hence eexpediting the timelines to their clinical trials."

Robert Lee, PhD, Senior Vice President, Business Development for PSI, adds: "A collaborative approach that may include co-investment in capabilities that we don't currently have offers risk mitigation for our client." One example is Agno building a single-product, sterile suspension commercial manufacturing PFS line on an exclusive basis for a client.

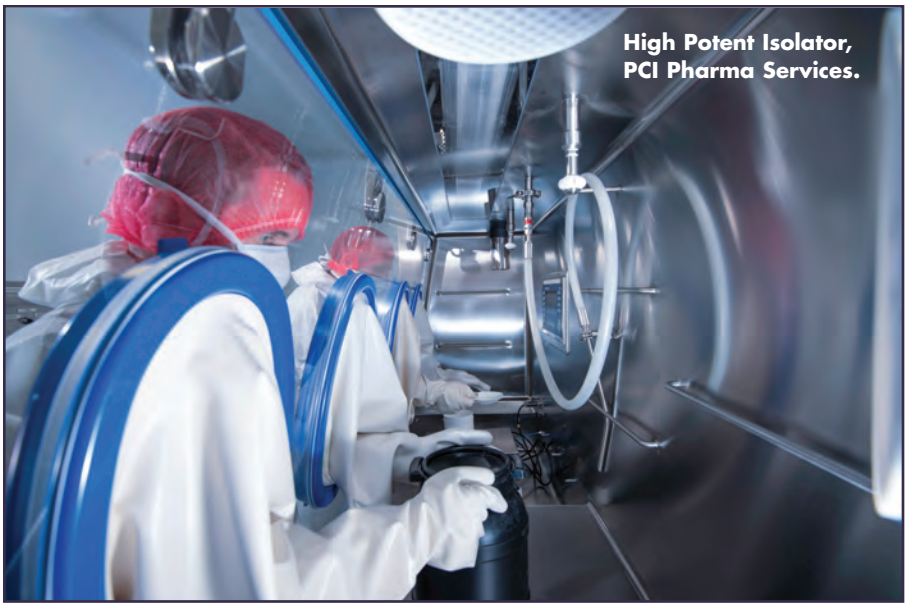
PCI Pharma Services: Fully Equipped Labs & Regulatory Support

PCI provides development and manufacturing services for both sterile and non-sterile dosage forms. Sterile services include formulation development (including complex formulations), lyophilization cycle development and optimization, geometric scale-up and process development, aseptic fill/finish, and lyophilization (plus non-aseptic, including bulk, medical device and intermediates), and bulk lyophilization. A recently expanded Contained Manufacturing Facility in the UK handles APIs to an OEL of 0.01μg/m3, with services including small- and large-scale granulation suites, Xcelodose® drug-in-capsule manufacturing technology, roller compaction, high-volume tablet compression and encapsulation, and oral liquids to support pediatric therapies.

Underpinning these core services are fully equipped analytical laboratories, extensive regulatory support, and a global distribution network for clinical and commercial supply. PCI has forged several key partnerships with equipment suppliers to ensure best-in-class technologies to support the development and manufacture of complex therapies. For example, PCI's partnership with S3 led to the recent supply of the Enclony Planet 6GP-TC High-Speed Tablet and Capsule Vision Inspection Machine, allowing visual inspection of tablets and capsules for clients.

Observation is indeed critical. There was a history of punch sticking observed during the development stage tablet compression of a drug product developed by PCI. Punch sticking occurs when powder material sticks to the punch face and leaves a defect on the tablet face, or material previously stuck to the punch face transfers to the next tablet causing a defect, explains David O'Connell, Director of Scientific Affairs, PCI. It's commonly caused by adhesive properties of the API or other materials in the formulation or by insufficient lubrication. The issue can be exacerbated by tooling design, in particular the design of the embossing.

"This issue was initially resolved by adjusting the amount of lubricant used during manufacture; however, when the tooling design was changed for the commercial image to create a debossing effect on the final tablet, the punch sticking issue re-emerged," he says. As additional lubrication can have a negative impact on product dissolution, the issue was resolved by adjusting the tooling embossing, and introducing chromium nitride coated tool-



High Potent Isolator, PCI Pharma Services.

ing, with support from the tooling supplier. The lubricant level was then further assessed during pre-validation trials to ensure process robustness prior to commercialization.

"A history of punch sticking is an important factor to consider when the drug product requires debossing," says Mr. O'Connell. "Certain characters or designs create a space on the tooling that can easily collect material through the batch compression." For example, characters such as; 0, P, A, and 4 are prone to the center portion of the character sticking to the punch. Tooling suppliers can often advise on alternative designs or considerations that minimize this risk, which becomes a key consideration if debossing is required for a drug product in tablet form.

Quotient Sciences: Helping to Accelerate Drug Development

Quotient Sciences provides integrated CDMO/CRO services to work for clients, ranging from candidate selection, drug substance synthesis and manufacturing, and preclinical formulation development, through to commercial drug product manufacturing. The company's flagship Translational Pharmaceutics® platform integrates formulation development, on-demand and adaptive GMP manufacturing, healthy volunteer clinical testing, data analysis and full regulatory support within a single organization.

"By controlling the full drug development value chain, including implementing adaptive clinical trial designs, we can transform the traditional model of drug development and accelerate a molecule on its route to market," says Dr. Andrew Lewis, Chief Scientific Officer, Quotient Sciences. "For example, within the First-in-Human (FIH) study, we can bridge from a fit-for-phase drug product to a POC-ready formulation. This reduces risk to the development program – something particularly powerful for drugs on accelerated approval pathways."

Artificial Intelligence also plays a role in accelerated pathways, having a notable impact in drug discovery. "Quotient Sciences is working with technology providers on applications that are 'quick wins' requiring minimal disruption, but with short-term impact on efficiency or productivity. We are also considering transformational, longer term use cases for AI, all aligned with our mission to accelerate drug development," says Dr. Lewis.

He adds that while there is no one-size-fits-all strategy to develop a drug, the desire to advance quickly through development is a common theme for nearly all. Programs should be designed to meet the needs of the client, molecule, and patient population. He says: "Using adaptive clinical trial designs in early development can help rapidly advance a fit-for-phase formulation to a POC-ready format, optimize performance of a drug product in response to emerging clinical data, and gain valuable data to inform the next stage of development."

Over the past 16 years, Quotient Sciences has conducted more than 500 Translational Pharmaceutics® drug programs, all ultimately resulting in expedited delivery of medicines to patients. A recent application was a collaboration with YourChoice Therapeutics in hormone-free family planning products.

"Having established a scale-up ready synthetic route for the YCT-529 API at our Alnwick, UK, facility, we developed the initial product formulation and the FIH clinical protocol in parallel," he explains. "Once approved, this allowed our Nottingham, UK, facility to perform on-demand drug product manufacturing for precision dose escalation, which removed extensive and costly up front product manufacturing. We are excited to see the potential of this first hormone-free male birth control pill as it progresses to patient trials."

Resilience: Technology & Processes Aim to Cut Timelines by 30%

Resilience provides customers with several solutions to route their program to the market. The company offers hands-on

support and regulatory guidance for development and drug substance manufacturing, and scale-up to commercial drug substance and drug product manufacturing. Resilience boasts an RFP process that aims to reduce timelines by approximately 30% compared to industry standards for First-in-Human materials, says Evan Pasenello, Vice President & Business Head – Biologics & Vaccines, Resilience.

Resilience is focused on a collaborative approach to partnership. One such partnership involved a complex therapy that required the development of a vaccine product containing aluminum adjuvants. Aluminum adjuvants (known as aluminum salts or alum) are added to many vaccines based on their ability to improve the overall potency, explains Milan Tomic, PhD, Senior Director – Process Development, Resilience. "For this program, Resilience employed its Process and Analytical Development division, which supports clients in designing their final drug formulation buffer. Their innovation resulted in a highly specialized system used when mixing the alum. The primary goal of the project was to ensure that the client could progress to clinic with a formulation that was appropriate to continue past Phase I and into later phases, with the ultimate goal of advancing towards a market-level formulation."

A client came to Resilience with a process that was too low yield to manufacture and commercialize in a cost-effective manner. The process development team resolved the issue by increasing the process productivity by almost a magnitude. "All of this was achieved in under three months by utilizing automated high throughput tools and our continuous high-density perfused batch (HDPB) process platform," says Ethan Bossange, Scientist I – Process & Analytical Development. "Continuous manufacturing is known for being flexible, reconfigurable, and having significantly lower cost of goods. However, the complexity of fully continuous biomanufacturing often brings lengthy development cycles, complicated control strategies, and new risks. Resilience's HDPB platform offers simplicity with a careful balance between speed to clinic, productivity gains, and risk mitigation."


Resilience brings together minds in science and engineering to deliver advanced technologies.

Risk is also mitigated with flexibility. Mr. Pasenello says that Resilience has designed a platform called ResIQ, which allows clients to complete a smart logic-based questionnaire that immediately generates a proposal for internal review. "The program is designed to continually adapt and collect the most relevant and important information to build an accurate and transparent guide as a first step to working with our team, whether your program is focused on process and analytical development or drug substance or drug product manufacturing," Mr. Pasenello says. "From there, dedicated business development, project management, and technical project leads are assigned to the program and serve as single points of contact and oversight throughout the project's lifecycle."

Resilience has strategically designed its digital ecosystem to focus on data enablement, aiming to provide both the company and its clients with a comprehensive, real-time perspective on operations and product lifecycle management. Such connectivity allows Resilience to trace lot and product genealogy. "This means that from any finished product batch, it is possible to access extensive lifecycle details, such as related experiments from process development, associated consumables and costs, resource allocation for development and manufacturing, pertinent quality data, physical storage locations, linked data files, and historian data," says Brian McNatt, Digital Sites Head – Research and Process & Analytical Development, Resilience.

Serán: Early & In-Depth Understanding of API Properties

Innovators are under increased pressure to reduce development timelines and deliver more challenging molecules. This molecular complexity includes increasing molecular weight, multiple active binding ligands (such as protein degradation and

molecular glues), and limited bioavailability due to decreasing solubility and permeability. This new reality requires an early in-depth understanding of API properties and formulation risks in order to develop a robust, scalable formulation.

"Serán's approach to developing early clinical drug product formulations has been successful in identifying over 50 FIH formulations, many of which have progressed to late-stage clinical trials without significant formulation changes, thus reducing the need for expensive API and time-consuming reformulation or scaleup trials and bioequivalence studies," says Rod Ketner, PhD, Vice President, Business Operations, Serán.

At Serán, collaboration begins with a tailored workplan to understand key API physiochemical properties – from a drug product delivery viewpoint – and identify opportunities and risks to development. The API characterization includes solid-state and materials testing, solubility measurements of both the crystalline and amorphous forms of the API in biorelevant fluids and may include salt and polymorph testing. Dr. Ketner says: "This hypothesis-driven approach leads to a science-based formulation screening to identify derisked technology selection and drug product formulations early in development."

If enabling technology is potentially required to achieve target drug exposure at projected doses, Serán's team screens a variety of formulation approaches using particle engineering. These approaches include API particle size control with dry or wet milling, use of functional excipients such as surfactants and acidulants, amorphous solid dispersions including spray dried dispersions (SDDs) and hot melt extrusion (HME), lipid formulation screening, and solid lipid nanoparticles. "All work is done with a material sparing approach, often requiring only a few hundred milligrams to fully characterize an API, select the technology approach, and screen amorphous SDD formulations, including supplying initial pre-clinical PK studies," he explains.

Oral solid tablet or capsule formulations are also screened using a material sparing, materials science-based approach that leverages experience, equipment, and characterization tools for direct compression or dry granulation-based formulations and manufacturing processes. The use of a dry granulation and tablet compaction simulator, and a representative granulator, enables facile and scalable formulation screening of prototypes that can be tested in biorelevant dissolution studies to ensure performance and screened for chemical and physical stability. This approach typically requires 5-25g, regardless of whether the API is crystalline or part of an enabled intermediate, such as an SDD. Lead formulations are then directly scaled, using material properties, to process scale equipment from Bohle, Gerteis, Korsch, O'Hara, and MG2. Compaction simulator, envelope density pycnometer, shear cell, and other tools characterize intermediates and finished dosage forms, including establishing ranges for manufacturing clinical trial material.

Dr. Ketner says: "Whether considering enabling technologies (particle size reduction, SDD, or HME), lipid formulations, or conventional approaches, Serán's team comprehensively assesses technology options rapidly with minimal API use to arrive at scalable drug product formulations and processes."

Simtra BioPharma Solutions: Collaborative Approach to Robust Molecule Production

Specializing in injectables, Simtra BioPharma Solutions supports products in all phases of development, from early clinical to commercial. The company handles complex, highly potent molecules (as well as standard molecules), and helps clients develop a formulation and then establish a manufacturing process that is robust, repeatable and scalable. Having its R&D and manufacturing co-located on the same campus helps expedite testing and minimize disruption of manufacturing, says Benoite Angeline, Vice President, Head of Marketing, Simtra BioPharma Solutions.

Serán's Leistritz ZSE 18 HP-PH Twin Screw Extruder for Hot Melt Extrusion and granulation.

"Many companies turn to us for the manufacturing of their ADC portfolios," she says. "Fill/finish of these products requires sterile and contained environment due to HPAPI in line with cGMP standards, which is capital intensive and requires specialized training of personnel. This is a growing segment of the market as seen by the acceleration in ADC approvals, the indication expansion for existing ADCs, and their use as both first and second line of therapy." Currently, Simtra has experience with more than 50 ADC projects that have been transferred into Simtra, including five commercial ADC programs.

She explains that Simtra BioPharma uses a collaborative, tailor-made approach for handling a multitude of molecule types with various toxicity profiles. The teams in tech transfer, supply chain, project management, quality, and R&D work collaboratively with each client to collect the information required for a successful transfer, and to communicate real time to help solve challenges and overcome hurdles that would cause delays. "Many clients come to us without an established process," says Ms. Angeline. "We try to learn as much as we can about our clients based on what we are provided, share whatever resources we have in our laboratories, in our manufacturing sites, and collaborate with them so that we can build a robust process that will lead to successful production."

Vial filling at Simtra BioPharma Solutions' Bloomington, Indiana facility.

Singota Solutions: Understanding the Needs of Small Biotechs

Singota Solutions specializes in providing formulation, analytical, and process development services to small biotech firms working in the injectables space. Singota understands the characteristics of its start-up clientele and has built its business structure to address these factors, explains Will Powers, Senior Director Business Development and Marketing at Singota. "Having a cGMP-compliant facility with storage, sampling and dispense, up-to-date analytical and manufacturing facilities are a must."

The use of robotics and the associated benefits of repeatability, increases in precision, and the reduction of human error increase the chances of project success and reduce timelines by avoiding delays caused by deviations. Manufacturing equipment designed specifically to minimize line loss, and techniques used in analytical methods and testing, can be devised to minimize the amount of API/drug substance/drug product consumed.

He says that personnel aligned with common goals across the organization, and competent, well-trained project managers who can inform and quickly coordinate a variety of moving parts from all sections of the organization helps move client projects along. "A predisposition to utilizing frequent and effective communication, and a collaborative, non-siloed approach to solving problems is important," Mr. Powers says. "The mindset and characteristics of the employees is critical. Having a team of smart, positive, disciplined, self-motivated employees with good interpersonal and teamwork skills at all levels of the organization makes for an organization that can get things done, and accomplish those tasks correctly."

One task that Singota recently performed was for a small biotech's formulation and process development project. A formulation change, which included adding a preservative, was identified by the client fairly late in the project timeline. This additive was identified as having compatibility issues with one of the polymers in use in the flow-path for aseptic filling. The Singota formulation and process development teams researched the problem, executed mixing and compatibility studies, and a workable solution was identified using the existing flow path. This enabled the project to be completed on time with the new formulation.

ten23 health: Leveraging Technology & Humans to Balance Development Parameters

ten23 health offers integrated services for the development, manufacturing, and

Singota Solutions of Bloomington, IN, specializes in aseptic filling, formulation, analytical, and process development services for small biotech firms in the injectables space. The cGMP-compliant facility features advanced robotics for precision, reduced human error, and minimized line loss, ensuring project success and faster timelines.

testing of sterile drug products. The company develops formulations, methods, manufacturing processes, and supports selection of primary packaging and device, provides stability material, and data. On the manufacturing side, ten23 can supply technical material, clinical, and commercial GMP materials.

"Our expertise is of specific value for complex formulations, such as high concentration formulations for subcutaneous or intravitreal use and highly precisely filled syringes, cartridges or vials – from preclinical to clinical to commercial stages," says Prof. Hanns-Christian Mahler, CEO Chief Enablement Officer at ten23 health.

ten23 health partners and collaborates along the value chain, supporting integrated into parenteral drug/device combination products with device specialists, such as SHL, West Pharma or Ypsomed.

"We partner with customers ranging from small academic spins or virtual startups to large corporate pharma companies, that we can equally support with our expertise and knowledge," says Dr. Mahler.

In collaboration with partner Elio, ten23 leverages artificial intelligence to support process design from a sustainability perspective. He says: "Additionally, ten23 leverages digital solutions, such as electronic lab journals (paperless lab). The company also utilizes the human to balance the various parameters for a highly customized outcome to ensure a sterile product designed for its very specific target parameters. Formulation Development is an art and science, requiring complexity management and problem solving, and understanding the interface of data with product design requirements, the human interface, and other important factors."

As a result, ten23 formulation programs are highly customized and tailored to the specifics of a given project, depending on molecule, target indication, quality target product profile and other criteria, while ensuring regulatory requirements. Dr. Mahler explains that the company supports customers with a variety of formulation and stability issues. Example include: understanding the degradation of surfactants in formulations and designing mitigation around this; tackling aggregation and particle issues in formulations; designing a formulation product to improve defects caused by lyo fogging; designing and assessing how the product can be administered safely to patients, while ensuring product stability (clinical administration setup and testing, CSTD evaluations); converting lyo products into liquid products by adequate formulation development; and developing subcutaneous and intravitreal-high concentration formulations (in syringes or cartridges) and converting from early-stage IV low-concentration formulations to later-stage development. ◆

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Drug Development EXECUTIVE

David O'Connell

Director of Scientific Affairs

PCI Pharma Services

PCI Pharma Services: A Consultative Approach to High Potency Formulation Development

Drug development is a very lengthy, expensive process. Reports indicate that for every single day a drug launch is delayed, millions of dollars in revenue can be lost, with estimates varying from $600,000 to $8 million per day.[1] Delays also lead to the suffering of patients who are unable to access the critical therapies in development to treat their condition. Ideally, this would not happen. But proper long-term due diligence on CDMO partners isn't always performed, leading to a suboptimal development and manufacturing strategy. As such, not only are delays a possibility, they are inevitable. *Drug Development & Delivery* recently interviewed David O'Connell, Director of Scientific Affairs at PCI Pharma Services, about why it's so important to choose the right CDMO partner to accompany you throughout the drug product lifecycle.

Q: What are the essential attributes of an industry-leading CDMO?

A: In terms of technology and manufacturing equipment, it's incredibly beneficial to work with a CDMO able to conduct small-scale development and manufacture (D&M), while also offering in-house scalability for late-stage clinical and ultimately commercial supply. This flexibility, and access to an extensive range of equipment and processes, ensures various challenges can be addressed, and the most suitable solution for each unique project can be found. A major benefit of in-house scalability is that no additional tech transfers are required; switching CDMOs throughout the product's lifecycle can be costly and introduces additional risk.

But equipment and facilities are only as good as their staff. Successful D&M requires strong cross-functional collaboration between highly experienced teams across a variety of disciplines, such as analytical, manufacturing, quality assurance and control and, of course, formulation development. A deep knowledge of their equipment and processes, and a strong awareness of alternative D&M methods, enables them to determine how various formulation attributes can impact the final drug product, both positively and negatively, and advise their sponsors accordingly throughout the process.

Understanding the CDMO's containment strategy is vital when outsourcing highly potent OSD programs. You need to understand the containment measures in place, and the level of potency the facility is able to handle safely. Oncology dominates the formulation development market with a 25% share in 2022, and an estimated Compound Annual Growth Rate (CAGR) of 8.3% to 2030.[2] Around half of oncology drug candidates contain highly potent APIs, so along with scalability and development capabilities, safe handling of these dangerous substances is a key consideration.

Q: What are the main challenges facing CDMOs during D&M programs?

A: Clients occasionally withhold critical reports and information about the product or overall project strategy, preventing their CDMO partner from analysing the data themselves and being able to develop a longer-term strategy for their product. This lack of transparency can lead to issues that surface when problems arise, making it difficult for the CDMO team to address them effectively. It also means the CDMO's processes are generated based on second-hand information, increasing the risk of critical information being missed by the CDMO.

Another challenge is the establishment of unrealistic or aggressive timelines, which can force the acceleration of development activities. This rushed approach may create problems during later stages of development and scale-up, potentially compromising the overall success of the project, as more formulation development may inevitably be required at a later, more time-critical stage.

Limiting the amount of development activity prior to the clinical trial manufacturing (CTM) stage can also pose difficulties. Of course, limited development can be the result of a limited budget, but open and honest discussions during the proposals stages enables the CDMO partner to advise what is possible within the sponsor's proposed budget.

Similarly, a limited supply of API can result in compressing multiple trials into a single batch. This reduces the usefulness of the data produced, making it challenging to draw meaningful conclusions from the results. Again, this can often be beyond the client's control, but it does have an impact on the quality of formulation development activities and the data gleaned during the process.

Q: What can sponsors do to maximize the efficiency of D&M programs?

A: Talk with your CDMO early to ensure the stability-indicating methods are optimized. CDMOs with the capability to develop methods in-house can work with you to execute multiple development activities in parallel. The more information you can share with the CDMO about your molecule, the quicker the development team can get your product to the clinic — and, of course, to commercial launch.

It's also essential to perform excipient compatibility and forced degradation studies upfront. These studies help identify potential incompatibilities or stability issues early in the development process, allowing for timely adjustments and mitigations.

Considering the scale-up process during development stages is also important. Doing so enables the formulation team to design processes that are more easily scaled, reducing potential challenges and delays during the transition from development, through clinical to commercial manufacturing. Considering scale-up early, along with clearly defined scopes of work, improves the workflow between the formulation and manufacturing operations teams within the CDMO, and contributes to a strong collaborative relationship between the CDMO and their sponsor — a relationship based on effective communication and a deep understanding of the long-term program goals.

Limiting the amount of development activity prior to the clinical trial manufacturing (CTM) stage can also pose difficulties. Inadequate pre-CTM development hinders the acquisition of robust process knowledge, which may lead to issues further into the project when it is less feasible to make modifications. Limited development can be the result of a limited budget; however, if open and honest discussions are held up front during the proposal stages, the CDMO partner will be able to advise what is possible within the sponsor's proposed budget.

Q: What trends have you noticed in the highly potent formulation development space?

A: A noticeable trend in the formulation development space is the use of a Design of Experiment (DoE)/Quality by Design (QbD) approach at earlier stages of the product lifecycle. DoE is a systematic, statistical approach with the aim of optimizing the product and the process by understanding the relationship between various factors (input variables) and responses (output variables). This method helps identify the most influential factors, determine their optimal levels, and establish robust and efficient processes while minimizing the number of experimental runs. During formulation development, multiple factors can influence the quality, safety, and efficacy of the final drug product, such as the choice of excipients, API concentration, processing conditions, and manufacturing equipment. Traditional trial-and-error methods can be time-consuming, resource-intensive, and may not identify the best combination of factors to produce a high-quality drug product.

DoE provides a deeper understanding of the interactions between factors and their impact on the final product, enabling the identification of critical process parameters (CPPs) and critical quality attributes (CQAs). By using a structured approach to experiment design, DoE allows for the simultaneous assessment of multiple factors and their interactions, reducing the total number of experiments required, which saves time and resources.

Q: Can you briefly describe a real-world case study in which D&M programs have been affected by poor strategy?

A: One customer had experienced issues related to powder static and poor flowability of the blend during the development phase. However, this critical information was not shared with PCI at the time. It only came to light when the client requested we use debossed tooling on the tablets. During the scale-up of the project using the new tooling, tablet splitting issues were observed halfway through the production run. The investigation into the cause revealed the client had experienced these issues during the development phase.

Powder characterization is essential, as it provides insights into critical powder properties, such as particle size distribution, morphology, density, and flowability. In this particular case, powder characterization of the blend during the development stage could have identified the issue with static and flowability, allowing the problem to be addressed during development rather than at the scale-up phase.

A thorough understanding of powder properties and their impact on processing performance is crucial for the successful development of solid dosage forms. Techniques, including particle size analysis, bulk and tapped density measurements, angle of repose, and shear cell testing, can be employed to assess the flow properties of a powder blend. With this information, formulation scientists can modify the blend composition or implement suitable processing techniques, such as granulation, to enhance the flowability and processing performance of the blend.

It's important to remember the right CDMO is there to help you achieve your clinical and commercial goals. They know their processes and equipment trains, and have a vast amount of experience in their areas of expertise. By identifying the right CDMO and establishing a strong collaborative relationship during the development stage, sponsors can rest assured their drug product will achieve speed to patient, study, approval, and commercial launch. ◆

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THERAPEUTIC FOCUS

The Unmet Need of Agitation in Alzheimer's Disease

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INTRODUCTION

Over 55 million people globally are currently living with Alzheimer's disease (AD). This number is expected to rise to 78 million in 2030 and 139 million in 2050 as the global population ages. AD is a hot space in the pharmaceutical industry: the newly FDA-approved drug Lecanemab and Phase 3 trial data from Donanemab have both demonstrated efficiency in reducing amyloid plaques in early stage Alzheimer's disease. These new drugs are encouraging for the medical community and patients alike; however, there are 2,000 patients a day who transition from mild to moderate dementia and begin to experience the associated neuropsychiatric symptoms for which there are severely limited research studies and treatment options.

There is a growing unmet need for the treatment of late-stage Alzheimer's disease. While preventative treatment early in the disease progression is the medical gold standard, it is simply not always possible (or financially viable). With late-stage disease comes neuropsychiatric symptoms, including agitation, depression, and sleep disorders. Up to 76% of Alzheimer's patients suffer from neuropsychiatric symptoms, including agitation, which is the clinical term for feelings of frustration often accompanied by actions of aggression as our loved ones become more disoriented during the moderate to late stages of the disease. Agitation is perhaps the most disruptive of the neuropsychiatric symptoms as it is associated with a higher likelihood of the patient being removed from the family home and placed in a care facility. Additionally, treatments at this stage of the disease become increasingly more challenging as the patient is disoriented, angry, and may react strongly to negative stimuli such as hospital trips and procedures with needles.

CURRENT STANDARD OF CARE FOR AGITATION IN ALZHEIMER'S

There is currently one approved treatment for agitation related to AD on the market, an antipsychotic that carries potential side effects of restlessness, dizziness, and an increased risk of death in older patients with dementia-related psychosis. Physicians may also prescribe antidepressants, anxiolytics, and antipsychotics "off label" to treat agitation, which can carry adverse side effects and compound the patient's disorientation as the medication levels are adjusted/adjusted.

The previously mentioned amyloid-targeting drugs are associated with brain bleeds and require invasive infusions, which simply aren't possible for aggressive, violent, or upset patients who refuse to travel to the facility, putting a significant burden on the family and caregivers. IGC Pharma (NYSE American: IGC) is developing a non-invasive treatment for agitation to relieve this burden.

IGC-AD1- A DIFFERENT APPROACH

IGC-AD1 has shown promising results in treating agitation in Alzheimer's patients. It is the first natural Cannabinoid-based investigational drug to be tested in human FDA trials for the treatment of AD. IGC-AD1 is an oral liquid solution, which would be an effective, simpler treatment option for patients. Furthermore, IGC-AD1 is a cannabinoid-based medication that has shown no severe reactions in Phase 1 clinical trials (https://www.clinicaltrials.gov/study/NCT04749563?intr=IGC%20AD1&rank=1).

IGC-AD1 is currently undergoing investigation in a Phase 2 clinical trial (https://clinicaltrials.gov/study/

NCT05543681). Interim results from the trail were recently announced in announced in March 2024, and demonstrated that patients dosed with IGC-AD1 had a more significant reduction in agitation, as measured by the Cohen Mansfield Agitation Inventory (CMAI), compared to placebo patients. Additionally, positive effects were observed as early as week two of the trial. At week 6 of the trial, the effect size of IGC-AD1 was measured at 0.66 compared to the placebo, with a p-value of 0.037 for combined week two and week six results. Overall, the interim data demonstrates a clinical and statistical reduction in agitation.

Unlike other pharmaceutical companies in the AD arena, IGC Pharma is pioneering participant diversity in this trial. Up to 12.5% of the aging population of Puerto Rico has Alzheimer's Disease, which is an increase from 10.7% of the continental US population, and yet there is a historical underrepresentation of Hispanic populations in clinical trials. In order to address this disparity, IGC has extended its clinical trial sites to include the University of Puerto Rico to increase participant diversity. There are additional plans to further expand the trial sites to Canada and Europe, while simultaneously identifying US trial site locations that offer the trials to underrepresented populations including African Americans and Indigenous Americans.

Additionally, the Phase 2 trial data analysis will involve innovative AI algorithms. During the trial, lifestyle logs are recorded for each patient. This log involves daily recordings of dietary habits, medications, blood pressure, and other factors. It is important for IGC Pharma to expand trial sites to international locations in order to assess any cultural or geographic relationship with lifestyle factors that may interact with IGC-AD1. The company will be using AI algorithms to detect patterns from the masses of data accrued in the daily lifestyle logs and uncover associations with lifestyle, ethnicity, AD biomarkers, neuropsychiatric biomarkers, epigenetic biomarkers and treatment success. IGC Pharma is pioneering a holistic approach to AD that encourages a deeper understanding of the patient as a person, which may have been lost in other studies of brain tissue and plaques.

MEETING THE SUPPLYING DEMAND FOR PLANT-BASED DRUGS

Supply chain issues have plagued the pharmaceutical industry throughout 2023, with no exception for cannabinoid-based therapies. In addition to the potential fluctuations with third-party manufacturing and transportation, the supply of medical-grade cannabis oil can be impacted by inconsistent lighting, refining, distillation, and purification, as well as insufficient quality analysis for potency, contaminants, and heavy metals.

As the first natural cannabinoid-based investigation drug being tested in

human FDA trials for the treatment of AD, it is pivotal for IGC Pharma to ensure that the IGC-AD1 supply chain is steadfast. IGC Pharma's vertically integrated business model is a key strategic advantage that is designed to drive quality control and efficiency in the business as it achieves key milestones and scale. In addition to the company's headquarters in Potomac, MD, IGC Pharma has a manufacturing and processing facility in Vancouver, Washington, and a research and development facility based near Bogota, Colombia. These facilities are designed to accommodate necessary testing and commercialization activities as IGC-AD1 progresses through FDA trials to Phase 3, and potentially commercialization.

These facilities integrate the key elements of the IGC-AD1 supply chain to help ensure the best quality product for the ongoing trials while simultaneously providing cost efficiencies, particularly as the company grows and requires more power and precision for extraction and distillation processes while adhering to pharmaceutical good manufacturing practices. Preparation for growth is key as demand for IGC-AD1 is likely to increase cumulatively as the population ages and AD diagnoses increase globally.

SUPPORTING DATA ON IGC-AD1

In Phase 1 clinical trials, IGC-AD1 was found to be safe, well-tolerated, and caused no serious adverse events. The studies found a clinically and statistically significant reduction in neuropsychiatric symptoms: the mean NPI Agitation and NPI-D scores decreased by 36% and 55%, respectively. These NPI Agitation and NPI-D scores indicate that IGC-AD1 may be efficacious at reducing agitation due to AD and associated caregiver distress. Apathy as measured by NPI-Apathy reduced significantly by 44.44%, 53.84%, and 49.88% in cohorts 1, 2, and 3 that received the medication once a day, twice a day and three times a day respectively. Additionally, IGC-AD1 did not show a risk of developing suicidal ideation or behavior as assessed by the C-SSRS in the mild to moderate AD population during the each of the 6-week trials. This is an important finding as many of the current antipsychotic treatment options list suicidal ideation as a possible side effect.

Additional investigations into patient diversity and metabolization of THC were undertaken, which found that Puerto Rican populations with increased polymorphisms in the CYP2C9 gene are susceptible to the accumulation of THC and its active metabolite and may experience prolonged elimination.

Murine model preclinical data also supports IGC-AD1's efficacy in treating

AD. The studies found that in Alzheimer's cell lines, the APIs in IGC-AD1 increased Aβ monomers and decreased Aβ aggregation in a dose–dependent manner. Second, the APIs in IGC-AD1 did not reduce Amyloid Precursor Protein (APP) levels in Alzheimer's cell lines. APP modulates cell growth, motility, and survival, and when levels decrease the small fragments eventually deposit as plaque. Third, in a Morris Water Maze test, mice dosed with the API in IGC-AD1 had significantly improved times and fewer errors than those in the control group demonstrating that memory improved in transgenic (APP/PS1) mice.

SUMMARY

AD is multifaceted and will require multiple treatment pathways for successful outcomes. As a response to the serious side effects produced by the current standard of care, IGC-AD1 is a testament to the potential of science, perseverance, and the power of nature. IGC-AD1, inspired by nature, is a drug with the potential to alleviate neuropsychiatric symptoms and the burdens of Alzheimer's disease. ◆

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

BIOGRAPHIES

Ram Mukunda is CEO and has played a pivotal role in IGC's executive leadership. In 2014, under his leadership, the company successfully completed a Phase 1 trial and is currently executing a Phase 2 trial. He responsible for the company's thrust into the pharmaceutical sector and its focus on Alzheimer's research, bringing a wealth of strategic expertise and vision to IGC. With a background encompassing BS in Mathematics and BS and MS degrees in Electrical Engineering, he actively shapes the company's strategy and oversees its international operations. Frequently traveling to various locations, he provides invaluable support to product and brand development initiatives, ensuring IGC remains at the forefront of innovation. His unwavering dedication is integral to achieving the company's long-term growth strategy objectives.

Evelyn Gutiérrez is a Chemical Engineer who graduated from the National University of Colombia and is pursuing her Master's degree in Epidemiology. She possesses a diverse educational background with additional training in Good Clinical Practices, Clinical Monitoring, Pharmacovigilance, and GMP. Accumulating approximately 9 years of professional experience, she has been an integral part of scientific and operational teams within multinational organizations. Since 2019, she has been a key member of the IGC Pharma team, where she has undertaken various successful projects. Notable accomplishments include the planning and establishment of a Research and Development laboratory and the acquisition of a license permitting the handling and utilization of controlled substances, specifically THC. She also played a pivotal role in the process of obtaining certification for the sale of cannabis-based oral formulations to patients.

Claudia Grimaldi is a Director and PFO at IGC. She leads an international team overseeing pre-clinical and FDA-registered clinical trials focused on Alzheimer's disease. Claudia's cost-effective strategies, involving prestigious international institutions, have reduced IGC's pharmaceutical R&D costs by over 50%. This enables IGC to fulfill its mission of providing affordable medications and products for conditions like Alzheimer's agitation, premenstrual syndrome, and dysmenorrhea. Her teams also ensure timely compliance with organizations such as SEC, FINRA, NYSE, IRS, FDA, IRB, and XETRA 2. Claudia holds an MBA from Meredith College, a BA in psychology from Javeriana University, and certifications from top business schools. She is fluent in Spanish and English.

CONTAINER PLATFORMS

Ready-to-Use Containers: Real Benefits, Important Challenges & Evolving Value

By: Gregor Deutschle and Gabriele Maier

INTRODUCTION

With injectable drug products, there are many different factors that must be carefully evaluated to develop an optimal aseptic manufacturing strategy. Among these many considerations, there is one critical decision that every CDMO can help their customer navigate: Which aseptic filling line is right for the product?

Container type has historically been one of the most decisive factors, as aseptic filling facilities have long relied on container-specific platforms designed to process bulk vials, syringes, or cartridges sterilized on-site. Today, however, a growing number of drug developers and drug manufacturers are shifting their attention to ready-to-use (RTU) container platforms: increasingly format-agnostic systems that process pre-sterilized containers delivered in fill-ready nest/tub or tray configurations. These platforms offer an added level of flexibility and efficiency that has made them a desirable option for many injectable drug owners.

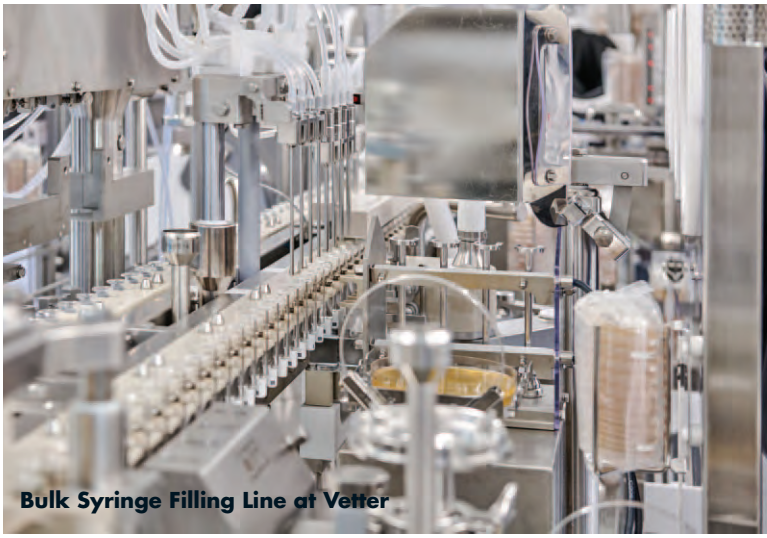
As a result, weighing the benefits of bulk and RTU container platforms has become an important step in developing an aseptic filling process. Each system type offers key benefits that are valuable for CDMOs and their customers to consider together. The following will look closer at some of those key benefits, dynamics driving the adoption of RTU container platforms, and several important areas of continuing evolution in the RTU market.

RTU ADOPTION DRIVERS

RTU container platforms are playing a fast-growing role in the global value chain for sterile injectables, with a projected value of $943.5 million USD by 2029 and a predicted 8.2% CAGR from 2023 to 2029.[1] Several factors have contributed to this market's growth:

Development Timelines: Today's drug developers face increasing pressure to get new therapies to market as quickly and efficiently as possible. RTU container platforms eliminate several time- and cost-intensive steps in the typical development cycle for sterile injectables, such as qualifying a sterilization process and developing a siliconization process for syringe- or cartridge-based products. Adopting these systems has become a valuable way to accelerate new products' overall path to market.

The COVID-19 Pandemic: The global surge in demand for COVID-19 vaccines also drove a spike in demand for systems that could be quickly and efficiently configured to process these injectable products. At the same time, this shift also created substantial demand for resources that could be swiftly adapted to



Bulk Syringe Filling Line at Vetter

process products displaced from their filling lines to make room for COVID-19 vaccines. Over the last several years, adopting RTU container platforms has been a valuable approach to addressing these related needs.

Diversifying RTU Container Formats: RTU container platforms have been in use for decades, but have historically been focused on processing pre-sterilized syringes. In recent years, suppliers have greatly expanded the range of container formats that these platforms can leverage. This step has made RTU container platforms a feasible option for a much wider range of injectable therapies, and a valuable resource for drug owners who want to maximize production flexibility across their products' life cycle.

Together, these dynamics and developments continue to drive both interest and investment in RTU container platforms – while also expanding the range of scenarios in which those platforms can be the right choice for a sterile injectable.

At the same time, however, conventional bulk filling lines continue to offer valuable benefits that CDMOs and their customers carefully compare with the advantages of an RTU-focused filling strategy. Let's take a closer look at these important considerations, and how they can inform an optimal choice of aseptic filling line.

FINDING THE RIGHT PRODUCT-PLATFORM FIT FOR A STERILE INJECTABLE

Depending on several factors – including market size, life cycle strategy, and more – both bulk and RTU container platforms can offer valuable benefits to consider when selecting an aseptic filling approach. Here are some important examples:

Handling Bulk Syringes at Vetter

Bulk Container Platforms: These well-established platforms are typically optimized for a single container type: vial, syringe, or cartridge. Many bulk container lines can also be readily adapted to many different variations of the format they process, enabling streamlined adjustment to different suppliers' containers.

With today's production technology, bulk container platforms are often an advantageous choice for vial-based products – particularly those with bigger production volumes. Vials frequently come in larger sizes, which reduces the number that can be placed in a tub of RTU containers and limits the speed at which pre-sterilized vials can be filled. Processed in bulk, this format is also typically easier to check-weigh without reducing line speed.

At the same time, bulk container platforms require both sterilization processes and infrastructure, such as washing areas and dry heat tunnels – all of which can add substantial development and validation time to a product's path to market. Switching container types also typically requires qualification and validation on a different filling line, steps that can add time and cost to key transitions in a product's life cycle.

RTU Container Platforms: In addition to eliminating sterilization processes, many RTU container platforms also substantially increase production agility – thanks to container-agnostic configurations that enable them to process multiple different container formats.

This feature allows products to be qualified and validated on a single filling line, and then remain on that line across multiple life cycle evolutions. Additional formatting and retooling steps are typically required to switch container type, and a significantly larger logistics area is usually needed to manage tubs and trays. But the cost of these requirements often compares favorably with migrating between high-speed bulk filling lines.

Due to their uniform, standardized container inputs, RTU container platforms can also be readily automated. Automating lines that process pre-sterilized containers can help minimize risks such as manual handling, container damage, and throughput disruptions.

Of course, these risks are ones that

Handling Pre-sterilized Syringes at Vetter

an expert CDMO can typically manage and mitigate with any selected filling line. Nonetheless, RTU container platforms remain a valuable option for drug developers who want to reduce development timelines, de-risk filling processes by design, and transition between container formats as efficiently as possible.

CONTINUING EVOLUTION: UNLOCKING THE FULL VALUE OF RTU CONTAINER SYSTEMS

Given the many advantages of RTU container platforms, it's likely that adoption of these technologies will continue to accelerate in the coming years. But while today's RTU-based filling lines already deliver substantial benefits – for drug developers and manufacturers alike – there are still several key considerations the industry will need to address to unlock the full value of RTU container platforms:

Inconsistent Outer Packaging: To enable automation and minimize manual handling, RTU container platforms require consistent, harmonized inputs that can be processed with minimal variation and unpredictability. Many suppliers are already supporting this need by adopting a uniform size for the tubs and trays in which pre-sterilized containers are delivered to aseptic manufacturers.

But at the same time, the outer packaging around those tubs and trays can often vary from supplier to supplier – and sometimes within lots from the same source. This variability is common with double-bagged configurations: tubs and trays with inconsistent exterior packaging can easily disrupt automated de-bagging processes, leading to costly delays and resets. This variability must be addressed and mitigated for RTU container platforms to consistently deliver on their full promise.

Environmental Impact: While pre-sterilized containers may offer many advantages, producing and using them does come with an added ecological cost. These containers are produced and processed using energy-intensive sterilization processes, and in configurations that generate a substantial amount of waste not associated with bulk container platforms – including a variety of tubs, trays, lids, and exterior bags.

Today, these components are typically non-recyclable and must be discarded. To support our industry's important sustainability goals, further research is required into potential solutions to the environmental challenges associated with adopting these more waste-intensive systems.

Supply Chain Limitations: Compared with filling lines that process bulk containers, RTU container platforms have substantially more exact and inflexible requirements for all container inputs. While most bulk container platforms can readily accommodate variations of the same container format, RTU container platforms can be much more sensitive to variability. They are typically configured to process vials, syringes, and cartridges that meet exact and unvarying specifications.

While uniform, standardized inputs can facilitate automation, this requirement can also add some latent risk to a product's supply chain. In the event of a disruption or backorder, it can be challenging for an aseptic manufacturer to identify an alternative supplier with containers that meet the same exacting specifications. Further harmonization of container formats will hopefully mitigate this challenge as the industry's adoption of RTU approaches accelerates.

While these are important considerations for today's sterile injectable stakeholders, collaboration and innovation will no doubt address each one in future evolutions of today's RTU container platforms. Mitigating these challenges will further enhance the impact of aseptic filling technologies that already make substantial contributions to the sterile injectable value chain – and further enhance our industry's ability to bring new drug products to market as efficiently and sustainably as possible.

LOOKING AHEAD: PURSUING THE FULL POTENTIAL OF RTU CONTAINER PLATFORMS

Holistically considered, RTU container platforms offer numerous advantages that are important to evaluate when developing an aseptic filling process – and that will give these technologies a robust and valuable role to play in the future of aseptic filling. We expect these technologies to soon become part of the manufacturing mix for many more injectable therapies, from niche indications to high-volume commodities.

At Vetter, we're already well-prepared to harness this trend, with ongoing investment in a range of RTU-specialized resources and infrastructure. At the same time, we're also pursuing the kind of strategic, forward-thinking sustainability strategies that our industry will need to address the environmental impact of RTU container platforms. With the right sustainability, regulatory, and standardization solutions in place, we're confident that these technologies can help our customers achieve the efficiency, sustainability, and quality we all hope to see in the biopharmaceutical value chain. ◆

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BIOGRAPHY

Gregor Deutschle is Director Product and Service Management. Since 2021, he has been responsible for the Product & Service management at Vetter. With his team, he takes care of matching the offerings of Vetter with the market demand and further advancing the business portfolio. This involves identifying market trends early on and verifying their potential impact on customer requirements, new products, and service needs. Prior to joining Vetter, he has worked in several roles from in-house consulting, project management, lean management, and business development. He has been working in the pharmaceutical industry for the last 12 years and started his career with a degree in Mechanical Engineering from RWTH Aachen University in 2008.

Gabriele Maier is Director/Production Site Manager at Vetter. She joined the company in 2006 after graduating with a degree in Food Science and Technology from the University of Hohenheim. She started in the department of Quality Operation and after 5 years, she switched to production and became a Production Manager at the Vetter Langenargen aseptic production plant where she gained experience with various products and bulk formats. In 2019, she was promoted to Site Manager. Then in 2021, she took over her current position of Director/Site Manager of the Vetter production site in Ravensburg South at which bulk and pre-sterilized systems are used in commercial production.

PFS MARKET TRENDS

Partnerships With Pharma Packaging Specialists Will be Key to PFS Product Success in 2024

By: Pieter Vercruysse

INTRODUCTION

The pre-filled syringe (PFS) market continues its steep growth trajectory. From a global market valuation of US $4.5 billion in 2022, it is anticipated to reach $5.53 billion by 2029, with a steady compound annual growth rate of 2.9%.[1] Looking ahead in 2024 and beyond, the secondary packaging chosen for PFS will play an increasingly pivotal role in steering the sector's development.

Essential to ensuring this anticipated growth is the successful integration of innovations into mainstream PFS packaging. Strategic advancements in design and manufacturing will benefit various pharma sectors, with a focus on developing solutions for enhanced user-friendliness in self-administration.

Despite the promising landscape, adopting novel PFS packaging presents a formidable challenge for many pharmaceutical entities, especially small-size drug developers. The capital investments necessary for upgrading manufacturing lines, coupled with the potential uncertainty surrounding the selection of optimal solutions tailored to the unique demands of treatments, can be a daunting hurdle in embracing new technologies.

To overcome these challenges in 2024, pharma companies need to establish close partnerships with specialists focusing on PFS packaging. This is critical for navigating obstacles and thriving in the evolving sector landscape.

The following examines the innovations set to transform PFS packaging in 2024 and outlines the benefits of partnering with packaging experts to craft patient-centric PFS products, ensuring security and success in the coming year.

PATIENT-CENTRIC SOLUTIONS: THE PFS USER EXPERIENCE

The self-administration of injectable medications has historically posed significant challenges for patients. The complexities involved in manually preparing syringes pose inherent risks of medication errors and contamination. These errors can arise from miscalculations in the preparation process that lead to compromised sterility or inaccuracies in dosage. Such issues present substantial obstacles to patient well-being, potentially causing adverse reactions or undermining treatment efficacy, emphasising the need for precision and safety in syringe preparation.

In response to the need for patient-centric solutions to enable more seamless self-administration, the pharmaceutical sector has dedicated substantial research and development resources to enhance the user experience. The development of the PFS has been a tangible outcome of these endeavours.

PFS presents pivotal advantages over the traditional vial and syringe approach. As PFS contain precisely measured single doses of medication, the risks associated with under- or over-dosing are effectively mitigated, ensuring a safer and more convenient user experience. This makes a PFS an optimal choice for patients who would otherwise need to visit a clinic to have medication administered. By using a PFS, patients can self-administer medication comfortably from home, eliminating the inconvenience of frequent clinic visits associated with traditional syringe methods.

UNLOCKING THE POTENTIAL OF SECONDARY PACKAGING

To unleash the full potential of PFS, it's crucial to have appropriate packaging. This ensures patients have what they need for accurate and safe treatment.

Beyond aesthetic appeal or providing a vessel for storing and transporting treatment doses, packaging plays a pivotal role in upholding the integrity of medicines, enhancing user convenience and supporting adherence.

Preserving Medicine Integrity

Packaging amplifies the value of PFS self-administration by helping to ensure patient safety in different ways:

- **Combatting Counterfeiting:** Drug counterfeiting poses a substantial threat to patient safety and the overall integrity of the global supply chain. Some 13.6% of medicines in low- and middle-income countries are estimated to be substandard or falsified, with this percentage increasing to 19.1% for antimalarials.[2,3] Those statistics, coupled with a 101% surge in counterfeit drug seizures during 2021 compared to the preceding year highlight the urgent challenge confronting pharmaceutical companies.[4] To address this, governments have implemented legal requirements for "serialisation" — unique identifiers on drug packaging to prevent falsified medicines from infiltrating the supply chain. Legal frameworks, such as the EU Falsified Medicines Directive (FMD) and the US Drug Supply Chain Security Act (DSCSA), Phase 2, establish the legal requirements for authenticity and traceability.

- **Ensuring Stability & Shelf-Life:** Secondary packaging must shield the primary packaging and, consequently, the product, from breakage and environmental exposure to ensure optimum shelf life. New advancements in packaging design are vital to maximise the stability and longevity of drug formulations. This is particularly the case now with drug products potentially having to travel long distances across international borders, which increases the risk of breakage or temperature excursions.

Facilitating User Convenience

Secondary packaging also contributes to greater convenience and comfort for self-administration by:

- **Streamlining Usability:** The right secondary packaging facilitates efficient kitting, allowing the incorporation of additional materials such as swabs, replacement needles, usage instructions and informative content. This enhances PFS useability, extending the range of injectable treatments that patients can self-administer.

- **Explaining to Patients How to Apply Their Treatments:** Clear labelling and easily understandable instructions are paramount for patients to prepare, inject and safely dispose of PFS. Providing straightforward guidance in the patient's language ensures a seamless self-administration process.

- **Ensuring Safety for Vulnerable Demographics:** With the rise of self-administration, the risk of children encountering hazardous drugs increases. Child-proof secondary packaging is crucial, preventing unsupervised access and ensuring safety.

ADVANCEMENTS FOSTERING PATIENT CENTRICITY & SAFETY

The potential advantages of secondary packaging for PFS extend beyond conventional benefits. The pharmaceutical industry increasingly acknowledges the untapped potential of packaging to elevate the patient centricity of PFS treatments.

Due to technological progress, several key innovations in secondary packaging are gaining prominence and are anticipated to be a central focus for new PFS products in the near future.

Smart Labels to Support Serialisation & Legal Compliance

In 2024, emerging solutions to support compliance with serialisation legislation may lie in smart labels featuring radio-frequency identification (RFID) or near-field communication (NFC) technology. These labels provide more robust information than traditional counterparts,

including unique identifiers and serialisation data critical for compliance with the latest regulations while facilitating seamless scanning during transport. Smart labels have the potential to harmonise data systems across the pharmaceutical supply chain, aligning serialisation compliance with operational efficiency.

Tamper-Evident Seals to Further Improve Patient Safety

Tampering, a concern linked to counterfeiting, poses a risk to patient safety. The alteration of packaging or labels can lead to substandard or falsified medications, jeopardising patient health. To address this, anti-tampering devices have been mandated in the EU for prescription medicines since February 2019.[5] Innovations over the next year aim to enhance these devices, ensuring any alterations are visible to patients and streamlining installation during filling and packaging.

Temperature-Sensitive Packaging to Support Cold Chains

Given the heightened sensitivity of biologics to environmental factors, there is a growing demand for temperature-controlled transit. The pharmaceutical cold-chain logistics market is anticipated to witness substantial growth, by $11.6 billion from 2022 to 2027, emphasising the importance of minimising temperature excursions.[6] Smart labels can potentially aid pharmaceutical companies by allowing real-time monitoring of temperature conditions during product transport. Processor cores within these labels can enable data transmission to a central database, allowing the identification and disposal of units with temperature excursions. This system aids in understanding the root cause of excursions, preventing future occurrences.

Kit Innovations Enhance Useability for Vulnerable Patients

Ongoing developments in kit packaging and associated manufacturing equipment aim to make PFS more user-friendly, especially for vulnerable patients. Alternative ergonomic grips can be packaged within kits, offering diverse options for patients, particularly older individuals with manual dexterity issues. These innovations empower patients with greater confidence in self-administering treatments, promoting independence and autonomy.

EMPOWERING PACKAGING THROUGH STRATEGIC COLLABORATION

Navigating the adoption of these innovations for the first time can be a daunting prospect, particularly considering the substantial capital expenditure required for equipment acquisition and installation.

To overcome these hurdles, an increasing number of pharmaceutical companies are forging strategic partnerships with expert contract packaging organisations (CPOs). In doing so, these companies can leverage the latest packaging innovations without the need for substantial individual investments. These strategic alliances are poised to alter the industry's trajectory, fostering efficiency and delivering enhanced patient experiences.

Equipped with the necessary infrastructure and capacity, CPOs play a pivotal role in supporting the industry in gaining early, efficient and effective access to innovations that support the launch of progressively patient-centric and complex dosage forms. Their ability to meticulously fill and seal high volumes of PFS in a sterile environment eliminates the need for pharmaceutical companies to invest in dedicated equipment themselves. This ensures compliance with rigorous regulatory standards, such as Annex 1 of the EU Guidelines for Good Manufacturing Practice, and guarantees the delivery of safe, high-quality and convenient products to patients.[7]

Beyond infrastructure, CPOs can provide pharmaceutical manufacturers with invaluable insights into the distinctive packaging requirements of their products. They offer flexibility and capacity to develop customised packaging services, adding tangible value for customers and establishing enduring partnerships.

Moreover, the collaboration between

pharmaceutical companies and packaging providers extends beyond operational efficiencies. CPOs contribute to improved branding and product promotion by aiding in the creation of packaging designs that resonate with target audiences. This collaborative approach effectively communicates product benefits, ensuring that these pharmaceutical innovations stand out in the competitive marketplace.

FINDING SUCCESS WITH THE RIGHT PARTNER

Seamless coordination between the sponsor pharmaceutical company and packaging providers right from the initial stages of product development is key to the success of any pharmaceutical product. This alignment is imperative for a complex dosage form like a PFS, given its intricate secondary packaging requirements. Early partnership is vital, especially for companies aspiring to leverage the advancements in patient convenience and supply chain security anticipated in 2024.

Starting collaboration from the project's inception allows manufacturers and CPOs to synergise their expertise. The fusion of expertise and capabilities optimises the cost-effectiveness, time efficiency, and sustainability of packaging designs, culminating in a process that streamlines time-to-market. Due to companies embracing this collaborative approach in 2024, a growing number of patients can benefit from novel treatments, enhanced by more efficient packaging solutions and delivered to market faster than ever before. ◆

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BIOGRAPHY

Pieter Vercruysse is VP of Customer Success and Supply Chain at Tjoapack. He joined Tjoapack in 2009 and has had several roles within the company, including QA/QP, Innovation Manager and Director of Operations. He is responsible for key account management, implementation of new products and processes, artwork, data management, and customer services. He earned a Master's degree in Pharmaceutical Sciences.

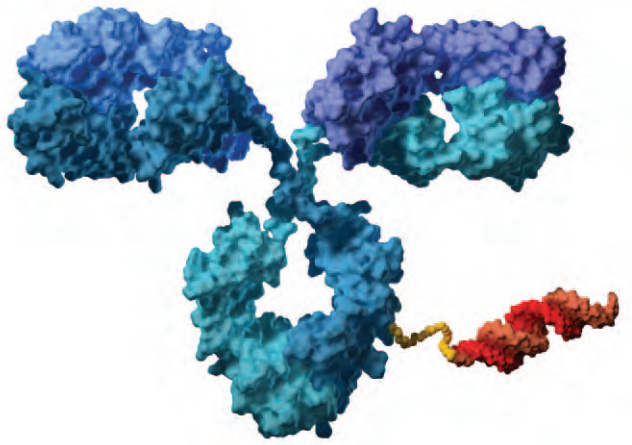
PLATFORM TECHNOLOGY

Antibody Oligonucleotide Conjugates (AOCs™) - Revolutionizing a New Class of Targeted RNA Therapeutics

By: Arthur A. Levin, PhD

INTRODUCTION

Therapeutic agents designed to modify the function of specific disease-related RNAs have been a promising approach in drug development for many years. Several recent advances in clinical research involving use of antisense oligonucleotides (ASOs) and small interfering RNAs (siRNAs) indicate that messenger RNA (mRNA) is a proven target for treating genetic diseases, including many rare diseases. These first-generation RNA-based therapeutics designed to target mRNA are often limited to diseases in which treatments must be delivered by local injection or by targeting the liver. With recent advances in RNA technology, including development of Antibody Oligonucleotide Conjugates (AOCs™), we now have the potential for RNA therapeutics to target new cells and tissues beyond the liver, a major challenge in the field in recent years. Broadening the range of tissues amenable to an AOC-based approach potentially enables the treatment of many more diseases than is possible with existing RNA therapeutics, including some conditions that affect larger patient populations. Avidity Biosciences recently demonstrated the first-ever successful targeted delivery of RNA to muscle in humans, a revolutionary advancement for the field of RNA therapeutics that may help transform the opportunities to advance research targeting many previously untreatable diseases in the years ahead.



Avidity Biosciences' investigational therapy del-desiran (AOC 1001) for the treatment of myotonic dystrophy type 1 (DM1) links a mAb (blue) to an siRNA (red).
[Photo credit: Avidity Biosciences]

AOCS™: BUILDING ON THE POWER OF OLIGONUCLEOTIDES

Researchers at Avidity Biosciences are building on learnings from ASOs and siRNAs that have represented major advances in the field of RNA therapeutics. Our team is creating a new class of RNA therapeutics called AOCs that have the potential to precisely target and modify the underlying genetic drivers of diseases. Our proprietary AOC platform is designed to combine the specificity of monoclonal antibodies (mAbs) with the precision of oligonucleotide therapies to target the genetic defects associated with a wide range of diseases.

The AOC platform is built from years of in-house engineering that integrates oligonucleotide therapeutics, modulation of RNA processes, antibody engineering and conjugation, and advanced drug delivery techniques. The broad flexibility of the AOC platform enables us to deploy various types of oligonucleotides, including siRNAs and phosphorodiamidate morpholino oligomers (PMOs), that can be engineered to modify RNA function in different ways to address specific disease processes. Examples include siRNAs that can reduce the expression of disease-related RNA, and splice-modifying oligonucleotides that can correct aberrant RNA processing. By marrying two validated technologies – mAbs and oligonucleotides – there is the potential to treat many more diseases than is possible with ASOs and siRNAs alone.

There are three key building blocks that comprise AOCs –

mAbs, oligonucleotides, and linkers. mAbs are advantageous because they have well-established safety profiles and high specificity and affinity that has supported their widespread use for more than 30 years. Our team engineers mAbs to be effector-function null and selects epitopes that are poised to achieve optimal activity levels. We are employing a mAb to the transferrin receptor in some of our lead clinical programs. Antibodies employed for future therapeutic programs by Avidity may use mAbs to different cell surface proteins as dictated by a disease we are targeting and specifically the target cell population.

When choosing the oligonucleotide component of AOCs, we consider several factors, including the underlying disease pathophysiology. siRNAs have shown benefits including favorable safety profiles (with no known thrombocytopenia, liver or renal toxicity), potency in the sub-nanomolar range, and sustained activity in both the cytoplasm and the nucleus. We select and modify siRNAs to diminish the risk of potential off-target effects post-administration, and we engineer them to enhance their efficacy, durability, and safety profiles. PMOs present similar advantages compared to siRNAs, including favorable safety profiles, potency in the nanomolar range, and sustained activity to promote exon skipping.

Known linkers are used to conjugate mAbs and oligonucleotides and are engineered to enhance their stability and durability. We also optimize several other key aspects of AOCs, including sites of conjugation and the ratio of oligonucleotides to antibodies. Together, these AOC building blocks offer distinct advantages including:

- Ability to target tissue and cell types beyond the liver
- Flexibility to select and deploy the most potent oligonucleotides
- Maximum therapeutic durability, enabling infrequent dosing
- Readily reproducible and scalable production

Avidity's AOC platform is built from years of in-house engineering that integrates oligonucleotide therapeutics, modulation of RNA processes, antibody engineering and conjugation, and advanced drug delivery techniques. [Photo credit: Avidity Biosciences]

Among all the advantages in this new class of drugs, the most important is the ability to target tissue and cell types beyond the liver, which have been generally inaccessible to RNA therapeutics. We are pursuing development of AOCs that may target tissue and cell types, including skeletal muscle, cardiac tissue, and immune cells. Our first AOC programs are from our muscle disease franchise and include clinical-stage programs in myotonic dystrophy type 1 (DM1), Duchenne muscular dystrophy (DMD), and facioscapulohumeral muscular dystrophy (FSHD). The results with AOC technology thus far show strong potential to target a broader range of rare and common diseases in the future.

TARGETED DELIVERY OF RNA INTO SKELETAL MUSCLE

There are a range of muscle diseases, including many rare diseases, in which optimal therapeutic activity can only be achieved by directly targeting muscle tissues where the underlying dysfunctional mRNA resides. Historically, this has been a significant challenge in the RNA therapeutics field. But a growing body of clinical and preclinical data show the potential of AOCs to overcome the limitations of other RNA therapeutics and successfully reach muscle tissue. In December 2022, data from a preliminary assessment of the Phase 1/2 MARINA® clinical trial in DM1 showed that Avidity's lead product candidate, delpacibart etedesiran or del-desiran (AOC 1001), achieved a historical first-ever event in the RNA field – successful targeted delivery of RNA to muscle in humans.

This revolutionary advancement provides evidence we can overcome a challenge that has eluded scientists for decades – the opportunity to target tissues beyond the liver with RNA therapeutics. This breakthrough milestone was only the beginning. Avidity recently announced two significant data readouts from the DM1 program. In March 2024, we reported new positive long-term data from the Phase 2 MARINA open-label extension (MARINA-OLE™) trial of del-desiran showing reversal of disease progression in people living with DM1 across multiple

endpoints, including video hand opening time (vHOT), muscle strength and activities of daily living, when compared to a matched END-DM1 natural history population over one year. The data also continue to demonstrate favorable safety and tolerability, based on more than 265 infusions totaling 61.1 patient-years of exposure. Also, in October 2023, we announced positive data of del-desiran demonstrating improvement in multiple additional functional measures including hand grip, muscle strength and patient reported outcomes in people living with DM1. These data were presented at the 28th Annual Congress of the World Muscle Society (WMS). These data augment previously reported positive data showing improvements in myotonia, muscle strength, and mobility reported at the American Academy of Neurology (AAN) Annual Meeting in April 2023.

Del-desiran continues to be assessed in the ongoing MARINA-OLE study in adults living with DM1. We are initiating the global pivotal Phase 3 HARBOR™ trial, a randomized, placebo-controlled, double-blind study to evaluate del-desiran in adults living with DM1, by the end of June 2024.

A FOCUS ON DM1

DM1 is an underrecognized, progressive, and often fatal neuromuscular disease that affects more than 40,000 people in the US and has no approved treatments that address the root cause of the disease. It is a complex, multisystemic disease that primarily affects skeletal, cardiac, and smooth muscle. Symptoms can vary from patient to patient but may include muscle weakness and myotonia (the impaired relaxation and prolonged contraction of skeletal muscle), respiratory and cardiac problems, fatigue, hypersomnia, severe gastrointestinal complications, and cognitive and behavioral impairment – resulting in a significant decline in quality of life.

DM1 is caused by an increase in the number of CTG triplet repeats found in the myotonic dystrophy protein kinase (DMPK) gene, which are toxic. In healthy individuals the number of repeats is approximately 35, but in people with DM1 there can be thousands. Del-desiran consists of a mAb that binds to transferrin receptor 1 (TfR1) conjugated with an siRNA that is engineered to reduce levels of DMPK mRNA in skeletal, cardiac and smooth muscle. The therapeutic hypothesis is that by reducing or inhibiting the formation of toxic DMPK mRNA, we can change the course of the disease in patients. This therapeutic approach may potentially address the spectrum of symptoms that people with DM1 experience. Del-desiran recently received FDA Breakthrough Therapy designation for the treatment of DM1. Del-desiran has previously been granted Orphan Drug and Fast Track designations by the FDA and Orphan designation by the EMA for the treatment of DM1.

ADDRESSING RARE MUSCLE DISEASES

Another advantage of the AOC platform is its flexibility. It has the potential to be used to develop multiple RNA-targeting therapies using similar principal components. Following successful targeted delivery of RNA into skeletal muscle, AOCs have further demonstrated their potential to treat muscle diseases in addition to DM1. Avidity is also advancing AOCs in the clinic that are designed to address the root cause of the rare muscle diseases DMD and FSHD.

DMD is an X-linked, irreversible, progressive disease caused by a genetic mutation that prevents the production of dystrophin, a protein that protects muscle cells from injury during contraction. The lack of functional dystrophin leads to stress and tears of muscle cell membranes, resulting in muscle cell death and progressive loss of muscle function.

Our AOCs are designed to promote the skipping of specific exons to allow the production of a functional dystrophin protein. There are many different exon mutations that can cause DMD, but our initial development efforts are focused on AOCs that can induce skipping for exon 44. There are currently no approved treatments for people with DMD amenable to exon 44 skipping (DMD44). DMD44 is extremely rare and affects approximately 900 people in the US (primarily boys).

AOC 1044 is an investigational therapy designed to deliver PMOs to skeletal muscle and heart tissue in order to skip exon 44 of DMD and enable dystrophin production. AOC 1044 is currently advancing in the Phase 1/2 EXPLORE44™ trial, a randomized, placebo-controlled, double-blind study in healthy volunteers and participants with DMD44. In December 2023, positive data from the EXPLORE44 study showed AOC 1044 delivered unprecedented concentrations of PMO in skeletal muscle with up to 50-times greater concentrations of PMO in skeletal muscle following a single dose compared to peptide conjugated PMOs in healthy volunteers. AOC 1044 was well tolerated, demonstrated statistically significant exon 44 skipping compared to placebo of up to 1.5% in healthy volunteers after a single dose of 10 mg/kg AOC 1044, and increased exon skipping in all participants. Avidity plans to provide a first look at AOC 1044 data in people living with DMD44 in the second half of 2024.

FSHD is another type of muscular dystrophy (one of the most common) for

which AOCs have indicated their potential as an innovative treatment approach. FSHD is a rare, progressive, and variable hereditary muscle-weakening condition marked by significant pain, fatigue, and disability. The disease is caused by the abnormal expression of a gene called double homeobox 4 (DUX4) and affects approximately 16,000-38,000 people in the US. Symptoms often begin in adolescence and early adulthood. Patients typically first present skeletal muscle loss in the face, shoulders, arms, and trunk, eventually progressing to the lower body. Many patients must eventually use a wheelchair for mobility. There are currently no approved treatments for FSHD.

AOC 1020 is an investigational siRNA AOC designed to reduce the expression of the DUX4 mRNA and DUX4 protein. Prior research suggests that even small reductions in DUX4 expression may lead to significant clinical benefit for patients. Taking advantage of the AOC platform, AOC 1020 utilizes the same mAb to deliver the therapeutic siRNA to muscle.

AOC 1020 is advancing in the Phase 1/2 FORTITUDE™ trial, a randomized, placebo-controlled, double-blind study in approximately 68 adults with FSHD. FORTITUDE will evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of AOC 1020 administered intravenously. Avidity plans to share data from a preliminary assessment of AOC 1020 in approximately half of study participants in the second quarter of 2024.

EXPANDING INTO OTHER CELL TYPES

Avidity continues to explore the full potential of the AOC platform through internal discovery efforts and research collaborations and partnerships. For example, we recently expanded our internal discovery pipeline to include new research and development candidates to treat conditions in skeletal muscle and cardiology. In November 2023, Avidity announced a global licensing and research collaboration with Bristol Myers Squibb, potentially worth up to $2.3 billion total, focused on the discovery, development, and commercialization of multiple cardiovascular targets leveraging the AOC platform. This new collaboration expands upon Avidity's existing collaboration with MyoKardia, a wholly owned subsidiary of Bristol Myers Squibb, that is intended to help expand our therapeutic activities to include cardiac-specific indications.

Beyond cardiology, we are exploring the use of AOCs in the treatment of immunologic diseases. We believe oligonucleotide therapies have the potential to address the challenges of immune responses at the RNA level. However, the ability to modulate immune responses has been hampered by the inability to deliver these agents to immune cells. By identifying and optimizing antibodies for specific immune cell types, our goal is to leverage the AOC platform to develop product candidates that can deliver siRNAs to disease-driving subsets of immune cells. Avidity is collaborating with Eli Lilly and Company initially on six mRNA targets in immunology and other select indications outside of muscle for the delivery, development, and commercialization of AOCs.

THE FUTURE OF RNA THERAPEUTICS

A rapidly growing body of evidence reinforces the significant promise of AOCs to address many areas of unmet need in health in entirely new ways, starting with skeletal muscle diseases. RNA therapeutics are a powerful approach when researchers are precise with targeting, which is only possible with expertise in molecular engineering and a comprehensive understanding of different disease pathophysiologies. By focusing on continued innovation in the RNA field, we are on the way to expanding the possibilities of RNA therapeutics and opening the door to new potential treatments for a wider range of patients in the years ahead. ◆

BIOGRAPHY

Dr. Arthur A. Levin serves as Distinguished Scientist and Strategic Leader at Avidity Biosciences and is a member of the Board of Directors. He previously held the position of Chief Scientific Officer at Avidity. He is a key opinion leader in the RNA therapeutics field who led teams responsible for the development of many oligonucleotides. Previously, he held the position of Executive Vice President of Research and Development at miRagen Therapeutics. Prior to that, he held senior drug development roles at Ionis (formerly Isis) Pharmaceuticals and Santaris Pharma. He has played key roles in the development of numerous oligonucleotides, including the first approved antisense drugs and the first microRNA-targeted therapeutic in clinical trials. He has a combined four decades of experience in all aspects of drug development from discovery through drug registration, both in large pharma and biotech companies. He has published more than 100 scientific articles and several of the most cited reviews in the field. He is on the scientific advisory boards of multiple institutions. He earned his PhD in toxicology from the University of Rochester and his bachelor's degree in biology from Muhlenberg College.

Technology & Services
SHOWCASE

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Adare Pharma Solutions is a global technology-driven CDMO providing end-to-end integrated services, from product development through commercial manufacturing and packaging, with expertise in complex oral formulations. Adare's specialized technology platforms provide taste masking, controlled release, solubility enhancement, and patient-centric dosing solutions. With a proven history in drug delivery, Adare has developed and manufactures more than 45 products sold by customers worldwide. For more information, visit Adare Pharma Solutions at **www.adarepharmasolutions.com.**

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Technology & Services Showcase

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Technology & Services Showcase

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