Drug Development & Delivery

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Analytical Testing

"The global market for pharmaceutical analytical testing outsourcing was estimated at $10.3 billion in 2023 and is projected to reach $16.3 billion by 2030. Rising complexity of drug molecules, particularly in the biologics and biosimilars sector, and a growing demand for personalized and specialized medicines, require more sophisticated analytical testing methods to ensure safety, purity, and efficacy, which often necessitate the use of highly specialized equipment and expertise."

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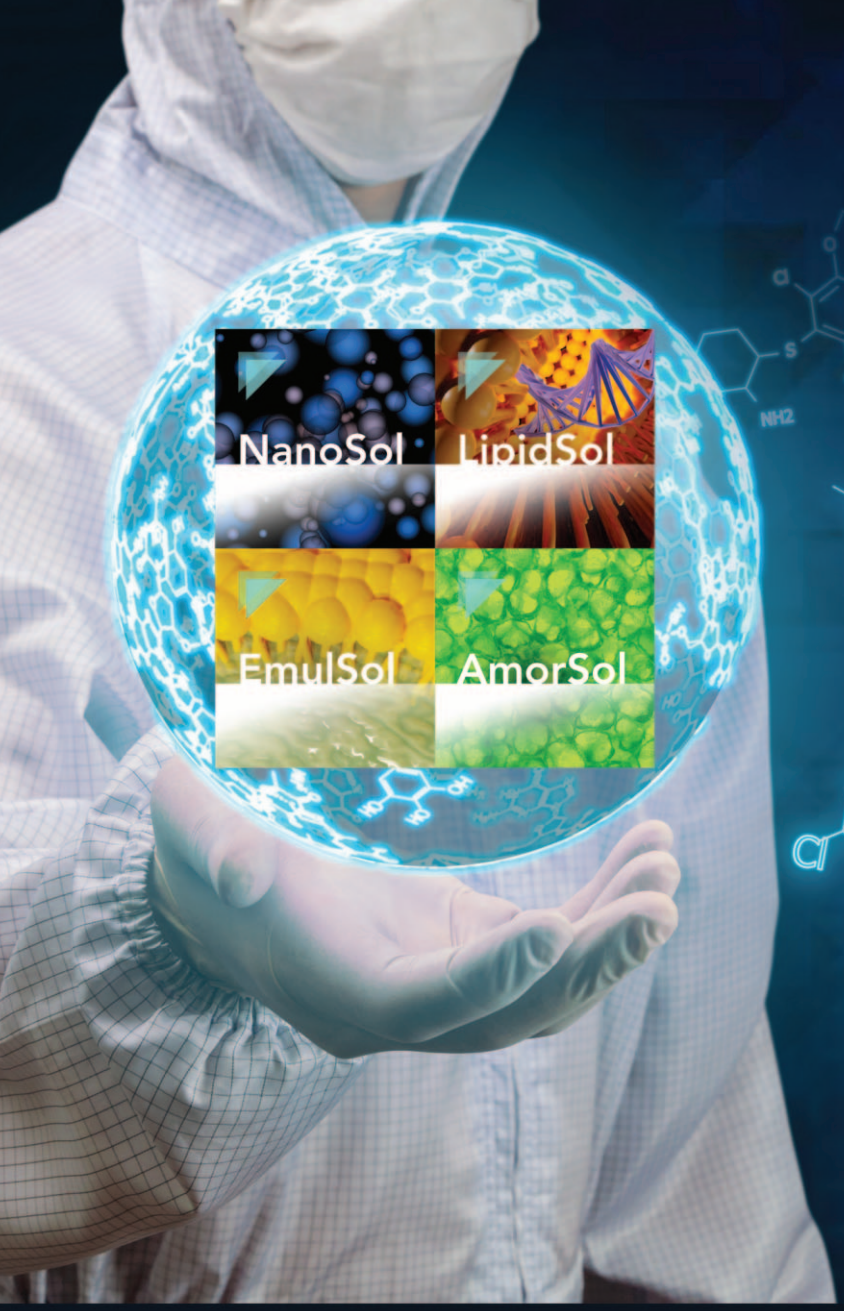

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Overcoming Drug Delivery Challenges

"The challenge of the BBB has spurred a wave of innovation, with scientists seeking new ways to circumvent this protective mechanism to deliver drugs effectively. One promising approach, focused ultrasound (FUS), is emerging as a revolutionary tool, enabling non-invasive, targeted BBB disruption. This method holds transformative potential in delivering therapies for neurodegenerative diseases and other challenging conditions, setting the stage for novel treatments in the years ahead."

p.69

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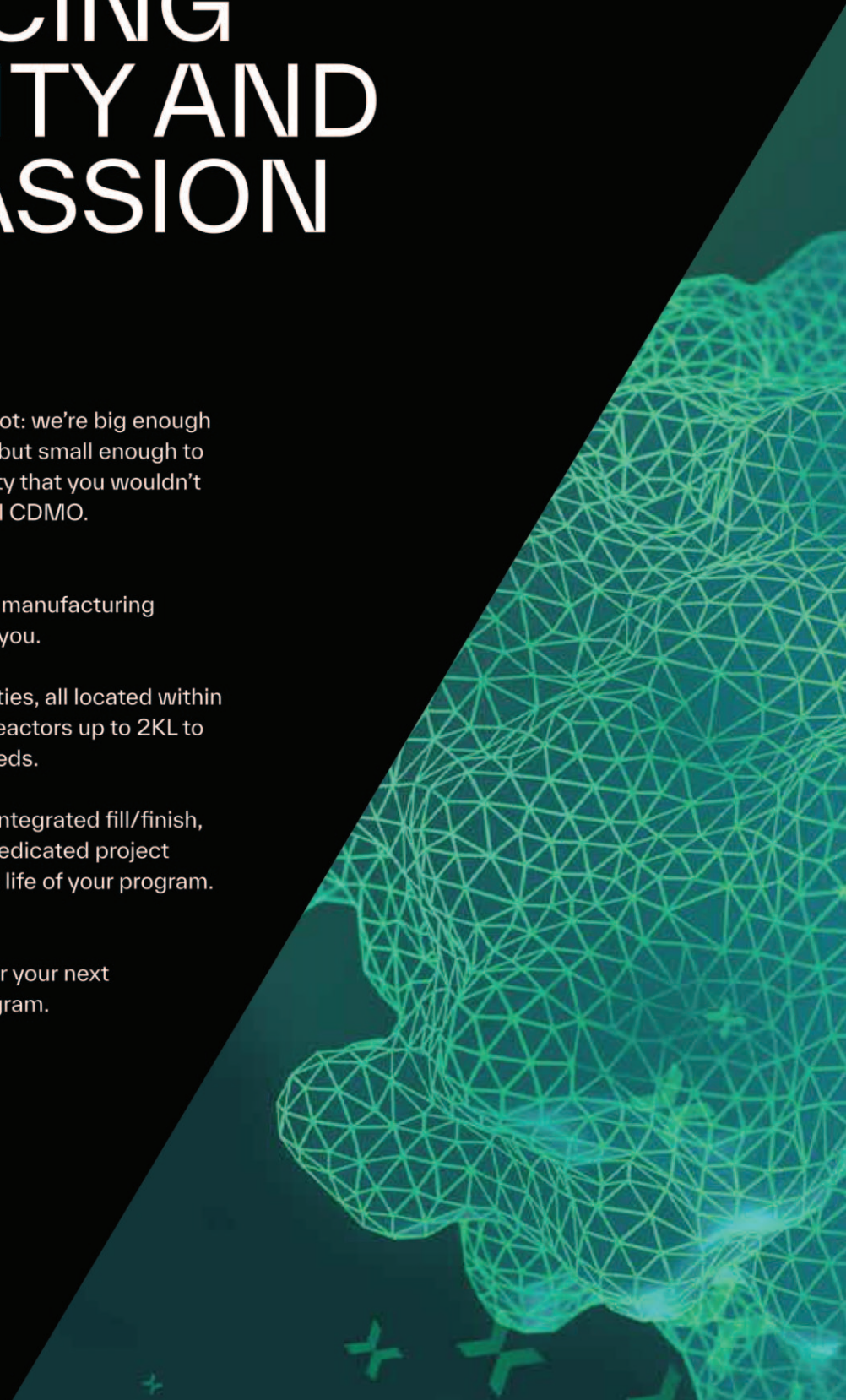

Ardena Completes Acquisition of Advanced Drug Product Manufacturing Facility From Catalent & Expands Bioanalytical Services in North America

Ardena recently announced it has successfully completed the acquisition of Catalent's state-of-the-art drug product manufacturing facility in Somerset, NJ.

This acquisition marks a significant milestone in Ardena's strategic expansion into North America, strengthening its capabilities in late-stage and small-scale commercial manufacturing of oral drug products and further integrating its comprehensive suite of drug development services.

The Somerset, NJ, facility encompasses over 50,000 sq ft of cGMP manufacturing space and is home to 200+ skilled scientists and technicians. It is a recognized Center of Excellence for advanced oral dosage forms, specializing in modified-release formulations, Hot Melt Extrusion for enhanced bioavailability, and the handling of controlled substances.

These capabilities complement Ardena's existing expertise in Europe, enabling the delivery of tailored solutions to pharmaceutical and biotechnology companies worldwide.

Additionally, Ardena has announced the expansion of its Bioanalytical Services in North America by opening a brand new bioanalytical lab at the Somerset facility. The initial investment will include a new 2,500+ sq ft lab, expected to be operational by Q3 2025, providing advanced analytical testing services for both small and large molecules, mirroring Ardena's European capabilities in immunochemistry, LC-MS/MS, flow cytometry, and qPCR platforms. This new state-of-the-art lab will provide enhanced support for global clinical trials programs.

"This acquisition reflects our ongoing commitment to supporting biopharma innovators at every stage of drug development," said Jeremie Trochu, Chief Executive Officer of Ardena. "The addition of the Somerset facility strengthens our ability to provide tailored, high-quality development and manufacturing solutions to our clients, while accelerating the international expansion of our fast-growing bioanalytical business."

Trochu added: "We are thrilled to officially welcome the Somerset team into the Ardena family. Their deep scientific and technical expertise, their impeccable regulatory track record, and unwavering dedication to excellence, align perfectly with our mission of helping clients bring life-changing treatments to patients quickly and efficiently."

The integration of advanced drug manufacturing and bioanalytical services in a single site in North America further empowers Ardena to accelerate the development of transformative therapies, reinforcing its commitment to innovation and client success.

Ardena is a specialist pharmaceutical Contract Development and Manufacturing Organization (CDMO) and bioanalytical Contract Research Organization (CRO) in precision medicine development of new, innovative, and complex molecules.

Ardena's mission is to enable current and next-generation therapies to get into the clinic and to patients faster.

Ardena assists biopharmaceutical companies in navigating through the drug discovery and development process, by providing integrated solutions including nanomedicine, drug product and drug substance development and manufacturing, solid-state chemistry, bioanalytical services, and CMC regulatory support.

March Biosciences Receives FDA Orphan Drug Designation for MB-105, a First-in-Class CD5 CAR-T Cell Therapy, for T-Cell Lymphoma

March Biosciences (March Bio), an emerging clinical stage biotechnology company committed to combating challenging cancers and other diseases, today announced that the U.S. Food and Drug Administration (FDA) granted orphan drug designation to MB-105, the company's first-in-class CD5-targeted CAR-T cell therapy, for the treatment of relapsed / refractory CD5-positive T-cell lymphoma.

"Beyond an important regulatory milestone, securing orphan drug designation for MB-105 from the FDA underscores the critical need for new therapeutic options for patients with T-cell lymphoma," said Sarah Hein, Co-Founder and Chief Executive Officer of March Biosciences. "Currently, patients with treatment-resistant or recurrent T-cell cancers face an extremely poor prognosis. The MB-105 Phase 1 trial has shown promising safety and efficacy signals in relapsed / refractory T-cell lymphoma patients. This designation further validates our development strategy as we prepare to initiate our Phase 2 clinical trial in early 2025."

The FDA's Office of Orphan Products Development grants orphan designation status to drugs and biologics that are intended for the treatment of rare diseases affecting fewer than 200,000 people in the United States. Orphan Drug designation provides various development incentives, including tax credits for qualified clinical testing, prescription drug user fee exemptions, and seven years of market exclusivity following FDA approval.

MB-105 is March Bio's lead program, launched from the Center for Cell and Gene Therapy (Baylor College of Medicine, Houston Methodist Hospital, Texas Children's Hospital). The company recently closed a $28.4 million Series A financing to advance Phase 2 development of MB-105 and strengthen its manufacturing capabilities to support future commercialization. Beyond MB-105, March Bio is advancing a robust pipeline of cell therapies to further expand its potential to improve treatment options for difficult diseases and malignancies.

MB-105 is a first-in-class autologous CD5-targeted CAR-T cell therapy in development for CD5-positive hematologic malignancies, including T-cell lymphoma (TCL), T-cell acute lymphoblastic leukemia (T-ALL), chronic lymphocytic leukemia (CLL), and mantle cell lymphoma (MCL). The therapy employs a proprietary CAR design that enables selective targeting of malignant cells while preserving some normal T-cell function. MB-105 is currently being evaluated in a Phase 1 clinical trial (NCT03081910) for relapsed / refractory TCL and T-ALL, demonstrating a 44% overall response rate in TCL patients.

Houston-based March Biosciences, launched from the Center for Cell and Gene Therapy (Baylor College of Medicine, Houston Methodist Hospital, Texas Children's Hospital), is dedicated to addressing challenging cancers unresponsive to current immunotherapies. Its lead asset, MB-105, is a CD5-targeted CAR-T cell therapy currently in Phase 1 trials in patients with refractory T-cell lymphoma and leukemia, with promising signals of efficacy and safety to date. A Phase 2 trial is expected to begin in early 2025. The company has raised over $52 million to date, inclusive of venture financing, support from the Cancer Prevention & Research Institute of Texas (CPRIT), and the NIH SBIR program.

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Northstrive Biosciences Signs Agreement for a Potential Breakthrough Obesity Therapy Targeting Fat Loss & Muscle Preservation in Combination With GLP-1

PMGC Holdings Inc. (formerly Elevai Labs Inc.) recently announced that its subsidiary, Northstrive Biosciences Inc., has executed a research agreement with a leading preclinical contract research organization (CRO) specializing in metabolic disorders. This Research Agreement will support a preclinical study carried out by the CRO and designed to evaluate EL-32, a novel engineered probiotic, as a monotherapy and in combination with the GLP-1 receptor agonist semaglutide, focusing on its impact on glycemic control and body composition in diet-induced obese (DIO) mice. Pursuant to the research agreement, within three months of completion of this study, the CRO will provide results of this study to Northstrive Biosciences and deliver a report to Northstrive Biosciences describing the work envisaged in the Research Agreement.

Northstrive Biosciences believes that EL-32 has the potential to treat obesity in combination with popular weight loss therapeutics, including GLP-1 receptor agonists, by preserving muscle mass while decreasing fat mass.

GLP-1 receptor agonists have gained prominence as effective weight loss therapeutics; however, research has shown that up to 40-60% of weight loss from these treatments comes from lean body mass, including muscle. This significant reduction in muscle mass underscores the critical need for strategies to preserve muscle during weight loss interventions.

Northstrive Biosciences' lead candidate, EL-32, is an engineered probiotic targeting dual myostatin and activin-A pathways – two clinically validated targets known to regulate muscle. By addressing these pathways, EL-32 has the potential to complement GLP-1 receptor agonists by preserving muscle mass while decreasing fat mass, offering a more comprehensive approach to obesity treatment.

The planned study, titled Effects of the test agent EL-32 administered either alone or in combination with semaglutide, on glycemic control and body composition in DIO mice, will use C57BL6/J mice as the experimental model. The study will evaluate body composition and metabolic progress across treatment groups receiving EL-32, semaglutide, or a combination of both. A leading preclinical CRO with extensive expertise in metabolic disorders and preclinical research will oversee the study's execution.

"We are thrilled to collaborate with a leading obesity CRO to advance our understanding of EL-32's therapeutic potential," said Deniel Mero, Co-founder of Northstrive Biosciences. "This agreement marks the beginning of an important phase of research to confirm the role of myostatin and activin-A pathways in preserving muscle mass while addressing the unmet need for muscle preservation during weight loss."

Northstrive Biosciences' existing preclinical data has demonstrated that EL-32 administration results in statistically significant improvements in key measures of physical muscular function and body composition. The planned study is expected to further validate EL-32's role as a therapeutic option that can be used in combination with existing GLP-1 therapies to treat obesity more effectively.

Northstrive Biosciences Inc., a PMGC Holdings company, is a biopharmaceutical company focusing on the development and acquisition of cutting-edge aesthetic medicines. Its lead asset, EL-22, is leveraging an engineered probiotic approach to address obesity's pressing issue of preserving muscle while on weight loss treatments, including GLP-1 receptor agonists.

SGS Introduces First Commercial Cell Sorting Service for the Biopharmaceutical Industry

SGS, the world's leading testing, inspection and certification company, is proud to announce the launch of Germany's first commercial cell sorting service via fluorescent-activated cell sorting (FACS) for the biopharmaceutical industry. This groundbreaking service leverages the advanced BD FACSAria™ Fusion system to support the development of advanced therapeutic medicinal products (ATMPs) and drive innovation in cell and gene therapy.

Previously available only in academic settings, this technology enables precise cell characterization and sorting using intra- and extra-cellular markers. SGS now brings this cutting-edge technology to the commercial market, allowing biopharmaceutical companies to access solutions tailored to the unique demands of ATMP development. In addition to the established and validated biomarker panels in immunology and oncology, their service also enables the development of customer-specific biomarkers and isolation of rare cell populations.

BD FACSAria Fusion is a state-of-the-art solution that enables seamless integration and significantly increases efficiency and flexibility during analysis. Equipped with four lasers and 16 fluorescence detectors, it allows the parallel measurement of thousands of cells and biomarkers, including rare populations. Its high-precision single-cell sorting capability can process up to 384 wells per plate. Beyond cell characterization, it also facilitates the isolation, cultivation and cryopreservation of rare cell populations.

SGS's FACS operations are conducted in a biological safety level 2 (BSL-2) genetic engineering facility, enabling the examination of genetically modified cells and significantly expanding the range of applications. This new capability allows the early identification of potential toxic effects and subsequent evaluation of therapeutic success.

Recognizing the importance of sample stability, SGS has also established a global, centrally coordinated network of laboratories to minimize transfer times between laboratories and clinical sites. This service is further enhanced by additional downstream applications, such as immunological and molecular biological procedures.

Germany, one of the largest markets for biopharmaceutical products in Europe, offers significant potential for innovation and growth, particularly in the field of cell and gene therapy. By integrating this service into its comprehensive suite of biologics testing services, SGS reaffirms its commitment to supporting biopharmaceutical research and the delivery of innovative, forward-looking solutions. With extensive expertise and advanced capabilities, SGS is uniquely positioned to lead the German market in accelerating patient therapies and ensuring the success of high-quality biotherapeutics that transform lives.

SGS is the world's leading testing, inspection and certification company. We operate a network of over 2,700 laboratories and business facilities across 119 countries, supported by a team of 99,250 dedicated professionals. With over 145 years of service excellence, we combine the precision and accuracy that define Swiss companies to help organizations achieve the highest standards of quality, safety and compliance.

Our brand promise – when you need to be sure – underscores our commitment to trust, integrity and sustainability, enabling businesses to thrive with confidence. We proudly deliver our expert services through the SGS name and trusted specialized brands, including Brightsight, bluesign, Maine Pointe and Nutrasource.

SGS is publicly traded on the SIX Swiss Exchange under the ticker symbol SGSN (ISIN CH0002497458, Reuters SGSN.S, Bloomberg SGSN:SW).

Leadership Panel

What Will Have the Most Impact on Drug Development in 2025?

By: Cindy H. Dubin, Contributor

Optimistic. That is the word 75% of global life science leaders feel about the prospects for the industry in 2025, according to a new report from the Deloitte US Center for Health Solutions.[1] This optimism is fueled by anticipated revenue increases, margin expansion, and advancements in technology that could lead to breakthrough innovation. This exclusive fourth annual *Drug Development & Delivery* Leadership Panel discussion asked life science leaders what they think will have the greatest impact on drug development in 2025.

Uwe Hanenberg
Head of Product Implementation
Recipharm

Eric Kaneps
Vice President, Sales & Marketing
Renaissance Lakewood, LLC

The Rise of Oral Biologics

The rise of oral biologics, fueled by the desire for more convenient administration, marks a significant step towards patient-centric drug delivery. This trend promises to enhance patient adherence and improve outcomes, particularly for chronic conditions like oral Insulin or oral therapies with innovative biologic compounds for Inflammatory Bowel Disease and Rheumatoid Arthritis, driving significant interest and investment.

Focus on High Potency APIs (HPAPIs)

The increasing prevalence of HPAPIs necessitates specialized handling, expertise, and manufacturing capabilities. This trend reflects the industry's focus on developing more targeted and effective therapies, often requiring smaller doses. Investing in HPAPI capabilities will be crucial for CDMOs and pharmaceutical companies to ensure the safe and efficient production of these advanced therapies.

Demand for Integrated Solutions

Pharmaceutical companies are increasingly seeking integrated solutions from their CDMO partners, streamlining operations and fostering greater efficiency through collaboration. This trend reflects a desire to reduce the number of suppliers and access comprehensive expertise from a single, trusted partner across the entire drug development lifecycle.

Development of Innovative Nasal Spray Device Technologies

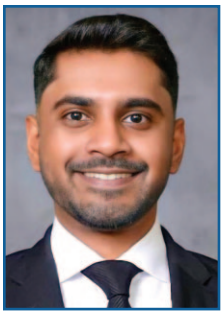
These devices offer improved usability, dose accuracy, and portability, leading to user-friendly devices that are easy to handle and minimize discomfort. Although this can improve patient compliance, developers must carefully consider nasal spray device selection. This can influence product performance and the patient experience. By leveraging nasal spray development expertise, companies can optimize device design, formulation characteristics, and product performance.

Availability of Funding for Startups

There has been a decline in funding over the past few years, following an initial surge before that, and the market is now starting to recover. This means that startups must carefully consider budgets and spend wisely. Here, partnerships with CDMOs can provide a potential solution. Partnering with a CDMO from the early clinical phases of a project all the way to commercialization is a solid strategy for maximizing budget and ensuring product progression. Expert CDMOs should be capable of offering support from pre-formulation and formulation development to validation and regulatory support and everything in between.

Artificial Intelligence

AI and other technologies will continue revolutionizing drug development by expediting drug screening and optimizing early-stage research. These technologies can enable the analysis of vast datasets, identify promising candidates and predict treatment response, ultimately accelerating the delivery of life-changing therapies.



Dr. Tony Thomas
Field Application Scientist
Ecolab Bioprocessing

Dr. Fiona Withey
CEO
TrakCel

Security of Supply

The secure supply of critical materials for drug development, including chromatography resins, has become critical in the wake of global disruptions such as the COVID-19 pandemic and geopolitical tensions. To address this, suppliers are diversifying production capabilities by investing in dual-continent manufacturing and prioritizing local sourcing, mitigating supply disruptions.

Greener Biomanufacturing

Regulatory pressures and societal demands will continue to drive innovation in greener biomanufacturing processes, and, as an industry, we must prioritize resources that are vital for life. Technologies that reduce water and solvent use, cut carbon emissions, and extend the lifecycle of raw materials are becoming integral to achieving both operational savings and environmental stewardship.

Cost Optimization

Cost optimization is paramount as patents on blockbuster biologics expire, creating opportunities to broaden access to biosimilars. However, increasing competition and demands from payers for lower prices are putting pressure on manufacturers to reduce costs. Innovations such as high-performance resins that can support process intensification strategies can enhance efficiency, reduce production costs and support the sustainable production of affordable biosimilars. These advancements are essential for balancing competitiveness with the goal of improving global access to medicines.

Commercialization of Cell and Gene Therapies

While reduced investment in CGTs became a common theme in 2024, there have been encouraging signs with recent announcements that we could be turning a corner. While we understand that investors need to see promising clinical data before making decisions, clinical data can only be generated if investors take a chance on early-stage companies with promising candidates. We hope to see renewed investor confidence in the promise of CGTs in early development in 2025. We are likely to see an increased focus on improving patient access to CGTs. A key part of this will be to ease the administrative burden of ordering these advanced therapies. The sector should look to technologies that can streamline workflows, improve collaboration, while safeguarding patient data. There are a multitude of orchestration platforms (software that tracks, manages and coordinates patient journeys for CGTs) currently available. Healthcare professionals at busy treatment centers may have to interact with several of these during a working day. Inconsistencies between platforms can lead to 'portal fatigue' for users. Standardization across platforms will help ease this frustration and boost efficiencies for the successful delivery of CGTs to patients.

Melanie Cerullo
Chief Quality & Regulatory Officer
ReciBioPharm

Expansion of the Advanced Therapeutic Medicinal Product

In 2025, we will see the expansion of the advanced therapeutic medicinal product (ATMP) sector, driven by the

development of novel gene editing technologies. Gene editing can provide transformative treatments for various conditions by addressing diseases at the genetic level. However, as a new therapeutic space, gene editing presents challenges for developers, including a steep learning curve, unique manufacturing requirements and limited access to costly production technologies. Complex ATMPs and gene editing products can suffer from supply chain constraints, with developers often relying on multiple partners to source raw materials, reagents and equipment. All-in-one CDMO solutions can help transform how gene editing therapies are developed and manufactured, reducing complexity and accelerating time-to-market.

More Strategic CMDO Partnerships

Taking gene editing as an example, CDMOs that specialize in mRNA bioprocessing or LNP production could partner with a sgRNA specialist CDMO to provide a complete solution from the same facility. These partnerships benefit developers as they create a single contract for all activities, simplifying development and manufacturing. ◆

Reference

1. 2025 life sciences outlook, Deloitte Center for Health Solutions, Dec. 2024, https://www2.deloitte.com/us/en/insights/industry/health-care/life-sciences-and-health-care-industry-outlooks/2025-life-sciences-executive-outlook.html.

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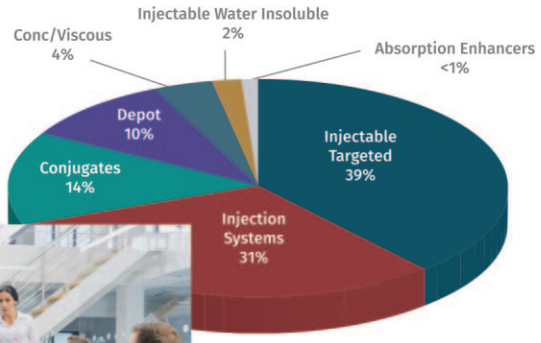
Evaluate New and Promising Technologies



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Assess Development Pipelines and The Competitive Landscape

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Formulation Forum

Nanoparticle Technologies for Oral Delivery of Peptides & Proteins

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

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Jim Huang, PhD
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INTRODUCTION

As we continue to embark on development of poorly soluble molecules for oral delivery, more specifically the large molecules like peptides and proteins, the solubility, permeability, and bioavailability challenges are surmounting. This is due, in part, to a lack of excipients and technologies to overcome these barriers stemming from appropriate stability and desired efficacy of drug molecules.[1] As the global market of peptide and protein drugs (PPDs) continues to gain market share to over $51 billion by 2027 with CAGR of about 9%, many of the drugs for treatment of metabolic diseases, such as the glucagon-like peptide (GLP-1) analogs liraglutide (Victoza®) and semaglutide (Rybelsus®), among others, will continue to fuel the growth in the future.[2] Ion pairing of polypeptides with negatively charges surfactants encapsulated in self-emulsifying drug delivery systems (SEDDS) will likely pave the way in oral delivery of innovative peptides.[3,4] Oral drug delivery technologies will therefore play a key role in transporting the drug through the epithelial membrane in the GI tract. Coupled with urgent medical needs, it will lead drug manufacturers to look for innovative oral delivery technologies for targeting cancers, diabetes, bacterial and viral infections, and other therapeutic areas.

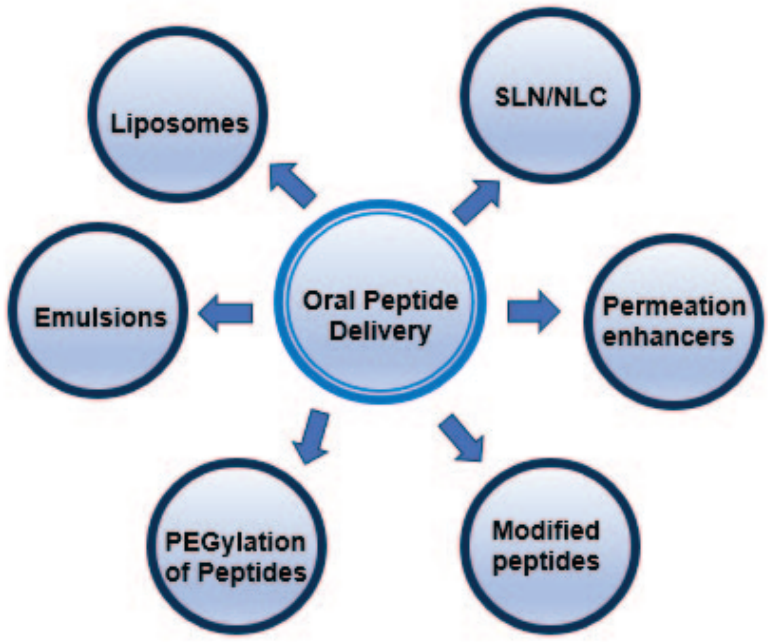
Oral bioavailability of PPDs falls below 2% mainly because of two reasons: 1) rapid degradation in the stomach and instability in the upper GI due to proteolytic enzymes and different pH conditions, and 2) poor permeability across GI membranes. On the other hand, colonic delivery benefits from lower enzymatic activities and around neutral pH, which could lead to improved absorption of PPDs through permeation enhancers. Nanoparticles could help protect these molecules from degradation and improve the permeation of PPDs.[5] Let's examine the nanoparticle technologies in oral delivery of large molecules.

NANOPARTICLE TECHNOLOGIES

Nanoparticles (NPs) ranging 1-100 nm in size are classified as liposomes; SLN, NLC, cubosomes, nanoemulsions, and microemulsions are widely recognized and well characterized for their lipids and polymers, structures, compositions, and physical properties. All these assemblies are aimed at improving solubility of Class II and Class IV drugs, as well for biologics and large molecules like peptides and proteins. Interest in NPs lies because they enhance solubility and also promote distribution and absorption of drugs through the intestinal epithelium in the GI tract.[6] There are, however, some challenges lie primarily with mucus barriers that inhibit the permeation of drug molecules. To overcome these challenges, hydrophilic polymers or lipid-based excipients can protect drugs from degradation as well as can lead to improved epithelial uptake. For example, polyethylene glycol (PEG), when used with insulin NPs, showed an improved epithelial uptake with controlled degradation of drug.[7] Lipid and surfactant-based NPs also demonstrate the enhanced uptake of drugs, and thus improve the bioavailability by several magnitudes while minimizing food effects.[8] NP liposomes with <150 nm in size comprised of insulin in novel lipids improved the stability and targeted the hepatocytes, leading to significant uptake of drug through the hepatic portal vein following oral administration.[9] In a clinical trial comparing the insulin vesicles and subcutaneous routes, it was observed that the oral bioavailability was markedly higher and it also significantly improved the tolerability and lacked any serious adverse effects.[10] These findings led to advancement of further clinical trials for Type 1 diabetes.[11] Figure 1 shows the possible routes for administration of oral peptides and proteins.

Another route for delivery of liquid formulations via the oral cavity for insulin is through RapidMist, which results in formation of micellar NPs stabilized with surfactants and permeation enhancers to maximize

FIGURE 1



NP Techniques Used in Oral Delivery of Peptides & Proteins

absorption and bioavailability. This device, so-called Oral-Lyn™, can deliver insulin to oral mucosa by micelles with a particle size of about 7 nm.[12] This product has been approved by the FDA for treatment of patients with Type 1 and Type 2 diabetes.[13]

PERMEATION ENHANCERS

These agents are a class of compounds added with the intent to facilitate the penetration of drugs through the gastric and intestinal epithelium. These compounds help permeate peptides and proteins through mucosal membranes in the oral cavity as well. Formulated with a chelating agent, protease inhibitor, and lipid excipients with abilities to encapsulate and protect, they can help protect PPDs from the GI tract and influence their absorption. A protein oral delivery (POD) system composed of EDTA (a chelating agent), bile salt as permeation enhancer, and protease inhibitor can help protect insulin from hydrolysis in the stomach as well as improve the stability in the small intestine, while also minimizing degradation. Insulin formulated in POD is highly effective in lowering glucose levels in Type 1 and Type 2 diabetes patients.

Medium chain triglycerides and surfactants are used as enhancers for oral drug delivery, and work in part by enzymatic hydrolysis that leads to generation of fatty acids and that helps improve the absorption via mucous permeation in GI tract. For example, medium chain fatty acid like caprylic acid, which comprises of 2%-3% in milk fat, has been found to enhance absorption.[14] Several other compounds, such as (N-5-chlorosalicyloyl)-8-aminocaprylic acid (5-CNAC), 4-(4-chloro-2-hydroxybenzoyl-amino) butanoic acid (4-CNAB), and N-(8-2-hydroxybenzoyl)-amino caprylic acid (SNAC) are also used as excellent permeation enhancers.[15] Table 1 lists a number of permeation enhancer technologies applied in oral delivery of marketed polypeptides.[16]

Citing a few examples: SNAC was licensed by Novo Nordisk from Emisphere Technologies, and used first in oral delivery of vitamin B12 and later in semaglutide (Rybelsus®) oral tablets because of its ability to enhance bioavailability, safety, and lack of impact on tight junctions. It is argued that SNAC protects by complexing semaglutide in the stomach and releasing the drug in a concentration-dependent manner as it interacts with the stomach mucosal membrane.[17] TPE™ technology used in formulation of Mycapssa® for oral delivery of octreotide showed significant bioavailability enhancement due to sodium caprylate, that acts as permeation enhancer, and its daily oral dose when compared with an injectable formulation was similar.[18]

Self-emulsifying drug delivery systems

TABLE 1

Delivery Technology/Company	Permeation Enhancer Composition	Oral Dosage Form
Precision olfactory delivery (POD®)/Impel Pharma	EDTA, Bile salts, soybean soy-bean trypsin inhibitor, aprotinin	Capsule
GIPET®/Merrion Pharma	Capric acid or mono-/di-glycerides	Capsule
Eligen®/Novo Nordisk	Salcaprozate (SNAC)	Tablet
Peptelligence®/Enteris Biopharma	Maltodextrin-coated citric acid, acylcarnitine	Tablet
Transient permeation enhancer (TPE™)/Chiasma Pharma)	Sodium caprylate	Capsule
Self-emulsifying drug delivery system (SEDDS)	Lipids, surfactants and co-solvents	Capsule

Oral polypeptides with permeation enhancers in approved drugs.

TABLE 2

Drug/Rx Name	Manufacturer/ Year	Technology	Indication	Pharmacokinetics
Octreotide/Mycapssa®	Chiasma/2020	Permeation enhancer	Acromegaly, neuroendocrine tumors	20 mg sublingual equivalent to 0.1 mg subQ, Cmax 22-33% lower than subQ, longer absorption time, food effect lower 90% absorption, half-life >2 h.
Semaglutide/Rybelsus®	Novo Nordisk/2019	Permeation enhancer	Type 2 diabetes	Oral dose 14 mg daily vs. 0.5 mg SubQ once weekly, max plasma conc. after 1 h, elimination half-life 1 week, 1% oral bioavailability
Oral Inhalation Insulin/Afrezza®	Mankind/2014	Technosphere® microparticles	Diabetes mellitus	Oral inhalation insulin, patient to patient variations 16% of AUC, 21% of Cmax, Tmax 10-20 min after inhalation, half-life between 120 and 206 min
Desmopressin acetate/Minirin®	Ferring Pharma/2008	Chemical modification	Central diabetes insipidus, nocturnal enuresis	BA 0.25% sublingual, Cmax 14, 30 and 65 pg/ml, Tmax 0.5-2 h, half-life 2 h
Cyclosporine A /Neoral®	Novartis/1995	Microemulsions	Immunosuppression	Oral bioavailability 29% higher than Sandimmune, 59% higher Cmax but comparable concentration in whole blood, terminal half-life increased from 6.3 h to 20.4 h

List of FDA-approved orally delivered polypeptides. These include a range of polypeptides, manufacturers, their indications, and enabling technologies.

(SEDDS) composed of lipids, surfactants, and co-solvents, self-emulsify in GI fluids to smaller droplets or emulsions and microemulsions. There are several small molecules that have been approved in SEDDS/SMEDDS.[19] In recent times, attention is also focused on delivery of oral peptides because of the ability for SEDDS/SMEDDS to enhance permeation through the mucus layer in intestine. Cyclosporine A is a marketed peptide approved as Sandimmune®/Neoral®. A SEDDS formulation composed of DMPG, Transcutol P, and a long chain triglyceride, led to high encapsulation and enhanced permeation of insulin via hydrophobic ion pair formation.[20]

ORAL POLYPEPTIDE APPROVED DRUGS

Table 2 lists the FDA-approved orally delivered polypeptides. These include a range of polypeptides, manufacturers, their indications, and enabling technologies.[21]

CLINICAL TRIALS

In spite of stability challenges with oral peptides and large molecules in gastric and intestinal pH conditions and due to proteolytic enzymes, innovation continues to find the optimized formulations to achieve greater stability and enhanced bioavailability. As previously described, polymeric excipients and solubilizers and permeation enhancers play an important role and as a result, only a few peptides and proteins are developed and launched. As the trend continues, there are several other candidates undergoing clinical studies. Table 3 shows some of the recent drugs undergoing clinical studies and the results still pending the outcome.

As shown in Table 3, Phase 1 human parathyroid hormone (1-34) is evaluated orally as RaniPill® (RT102) single dose in women volunteers in comparison with 20 mg subcutaneous dose of Forteo®.[22] In another study, oral EB612 (EBP05) is investigated for hypoparathyroidism in a single daily dose of PTH (1-34) in comparison with SubQ dose of 100 mg of NATPARA PTH (1-84). In another study, Ovarest® (Leuprolide) 60-120 mg daily dose oral tablet is investigated in women with endometriosis in comparison with Lupron Depot for treatment of endometriosis.[23]

SUMMARY & FUTURE PERSPECTIVES

With few exceptions, many of the peptides and proteins are unstable in gastric and intestinal pH, and possess low permeability and absorption; therefore, these are commonly administered parenterally. Due to their inherent limited permeability and solubility, the industry continues to evaluate innovative technologies as well as to align with the desired pharmacological outcomes via oral delivery by modifying the structural changes. Permeation enhancers could play a crucial role to help facilitate the transport through gastric or intestinal epithelium membrane, leading to absorption via paracellular or transcellular routes. Nanoparticles composed of surfactants,

TABLE 3

Study	Study Type	Details	Start Date
Entero PTH (1-34) (EB612(EBP05)	Randomize, active, partial cross-over design	Dosed in patients with primary hypoparathyroidism	June 2018
RT-102 PTH (1-34) oral formulation	Prospective, single center open label, Phase 1	PTH dosed oral via RanPill® capsule	February 2022
Ovarest® Leuprolide	Open label, Phase 2	Establish efficacy and pharmacodynamics	March 2022

Clinical studies of peptides.

medium chain fatty acids and triglycerides, and bile salts could temporarily affect the membrane integrity through their lipophilicities and hence could lead to increase in permeability. Taken together, it is obvious that a drug's permeability and absorption through nanoparticles composed of lipids and/or surfactants via epithelial membrane will help improve the oral bioavailability of PPDs. As illustrated in Figure 1, the oral absorption of PPDs occurs through several routes. Thus, finding the right approach to an induvial polypeptide in NPs, stable for an extended period while transit in GI tract, remains the biggest challenge. Ascendia's enabling platform technologies, AmorSol®, NanoSol®, EmulSol®, and LipidSol® could be explored for innovative large molecules in oral delivery of peptides and proteins. With its state-of-the-art cGMP manufacturing capabilities, Ascendia can lead the way for designing and manufacturing of drugs for oral delivery of PPDs. ◆

REFERENCES

1. S. Ali and K. Kolter, Challenges and Opportunities in Oral Formulation Development, Am. Pharm. Rev., December 2012.
2. FDA. Novel Drug Approvals for 2020, www.fda.gov/drugs/new-drugs-fda-cders-newmolecular-entities-and-new-therapeutic-biological-products/ novel-drug-approvals-2020/.
3. V. Claus, H. Spleis, C. Federer, K. Zoller, R. Wibel, F. Laffleur, C. Dumont, P. Caiss, A. Bernkop-Schnürch, Self-emulsifying drug delivery systems (SEDDS): In vivo-proof of concept for oral delivery of insulin glargine, Int. J. Pharm., 2023, 63, 122964. https://doi.org/10.1016/j.ijpharm.2023.12296.
4. C. Menzel, T. Holzeisen, F. Laffleur, S. Zaichik, M. Abdulkarim, M. Gumbleton, and A.B. Schnurch, In vivo evaluation of an oral self-emulsifying delivery system (SEDDS) for exenatide, J. Contr. Rel., 2018, 277, 165-172.
5. J. Zhong, B. Xia, S. Shan, A. Zheng, S. Zhang, J. Chen, and X. Liang, High-quality milk exosomes as oral drug delivery system. Biomaterials 2021, 277, 121126.
6. C. Dumont, S. Bourgeois, H. Fessi, and V Jannin, Lipid-based nanosuspensions for oral delivery of peptides, a critical review. Int. J. Pharm., 2018, 541, 117–135.
7. Y. Zheng, J. Wu, W. S. Lei, W. Rui, Z. Min L. Yi, C. Minglu, Z. Zhirong, and Z. Y. Huang, Multifunctional nanoparticles enable efficient oral delivery of biomacromolecules via improving payload stability and regulating the transcytosis pathway. ACS Appl. Mater. Interfaces, 2018, 10, 34039–34049.
8. S. Noble and A. Markham, Cyclosporin: a review of the pharmacokinetic properties, clinical efficacy and tolerability of a microemulsion-based formulation (Neoral®). Drugs, 1995, 50, 924–94.
9. E. Harris, An industry update: the latest news in therapeutic delivery. Ther. Deliv., 2017, 8, 939–946.
10. W. B. Geho, H. C. Geho, J. R. Lau and T. J. Gana, Hepatic directed vesicle insulin: a review of formulation development and preclinical evaluation, J. Diab. Sci. Tech., 2009, 3, 1451-1459.
11. Diasome. Rethinking Insulin, www.diasome.com/breakthrough-hdv-technology/.
12. P. Pozzilli, P. Raskin, and C. G. Parkin, Review of clinical trials: update on oral insulin spray formulation. Diab. Obes. Metab., 2010, 12, 91–96.
13. Clinical Trials Arena: Oral-Lyn- oral spray formulation of human insulin for Types 1 and 2 diabetes, www.clinicaltrialsarena.com/projects/oral-lyn/.
14. S. Maher, R. J. Mrsny, and D. J. Brayden, Intestinal permeation enhancers for oral peptide delivery. Adv. Drug Deliv. Rev., 2016, 106, 277–319.
15. C. Kapitza, E. Zijlstra, L. Heinemann, M. C. Castelli, G. Riley, and T. Heise, Oral insulin: A comparison with subcutaneous regular human insulin in patients with type 2 diabetes. Diab. Care, 2010, 33, 1288–1290.
16. A. T. Zizzari, D. Pilatsika, F. M. Gall, T. Fischer and R. Reidl, New perspectives in oral peptide delivery, Drug Discovery Today, 2021, 26, 1097-1105.
17. S. T. Buckley et al. (2018) Transcellular stomach absorption of a derivatized glucagon-like peptide-1 receptor agonist. Sci. Transl. Med., 2018, 10, eaar7047.
18. Melmed, S. et al. (2015) Safety and efficacy of oral octreotide in acromegaly: results of a multicenter Phase III trial. J. Clin. Endocrinol. Metab. 100, 1699–1708. DOI: 10.1126/scitranslmed.aar704.
19. S. Ali and K. Kolter, Tackling the challenges with poorly soluble drugs, J. Anal. Pharm. Res., 2015,1(1), 1–3.
20. T. Karamanidou, K. Karidi, V. Bourganis, K. Kontonikola, O. Kammona, and C. Kiparissides, Effective incorporation of insulin in mucus permeating self-nanoemulsifying drug delivery systems. Eur. J. Pharm. Biopharm., 2015, 97, 223–229.
21. M. Nicze, M. Borowka, A. Dec, A. Niemiec, and L. Bulkak, The current and promising oral delivery methods for protein- and peptide based drugs, Int. J. Mol. Sci., 2024, 25, 815.
22. A Phase I Study to Evaluate the Pharmacokinetics of Parathyroid Hormone (1-34) Administered Orally via RaniPillTM Capsule. https://clinicaltrials.gov/study/NCT05164614?term=nct05164614&rank=1#study-overview.
23. An Open-Label Dose-Finding Study to Evaluate the Pharmacodynamic (PD) Profiles and Efficacy of Different Dosing Regimens of Leuprolide Oral Tablets (Ovarest®) in Women with Endometriosis https://clinicaltrials.gov/study/NCT05096065?term=nct05096065&rank=1.

MICRONEEDLE MANUFACTURING

The Value of a Manufacturing-Oriented Microneedle Mindset

By: Andrew Riso

INTRODUCTION

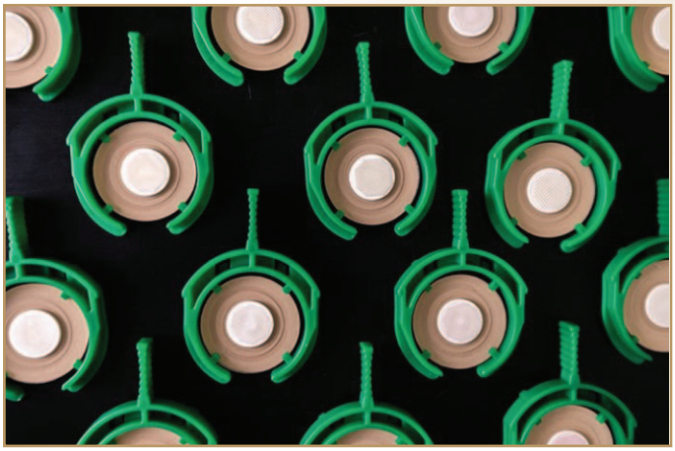
Microneedle array patches (MAPs) are at the forefront of drug delivery innovation, with the potential to revolutionize how medications and vaccines are administered. These patches offer the potential to combine the ease of transdermal application with the efficacy of injections, providing a more intuitive method of drug delivery for a wide range of therapeutics.[1]

However, despite the significant buzz surrounding microneedle technology, a considerable gap remains between innovations and market-ready products. While early stage development and preclinical studies have shown promising results, the challenge of translating these advancements into scalable, commercially viable products persists.

To bridge this gap, a shift in mindset is crucial. From the start of the process, researchers, biotech companies, and manufacturers can benefit from adopting a commercialization-focused approach. This means considering not just the initial innovation but also how that technology will translate to GMP clinical production and eventual commercial-scale manufacturing. Thinking ahead is essential for minimizing risk and attracting the investment needed to bring microneedle array patch products through late-stage clinical trials and to market.

THE CURRENT STATE OF MICRONEEDLE TECHNOLOGY

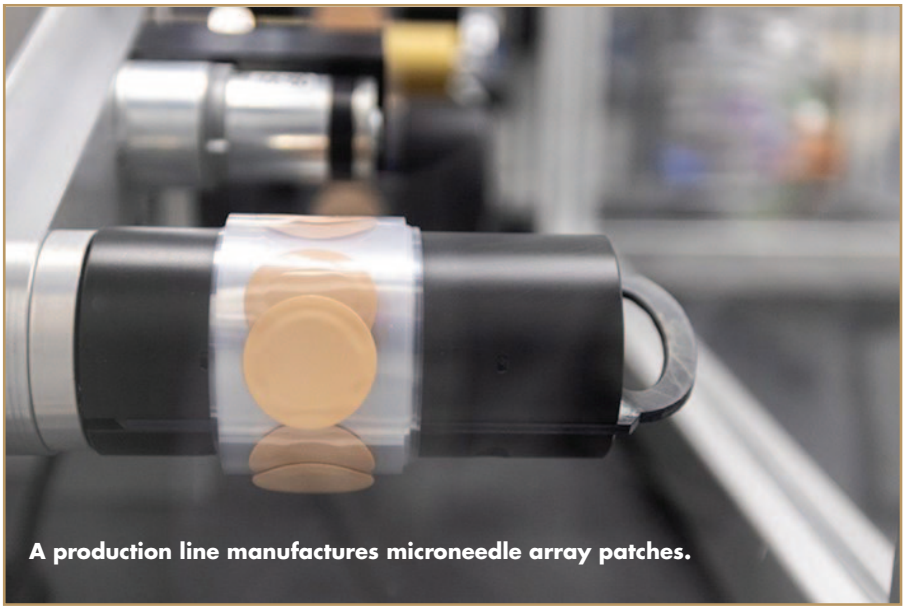
Recent years have seen a diversification of microneedle types, opening possibilities for addressing a broader range of



therapeutic applications and patient needs. Based on data from www.clinicaltrials.gov, these platforms have been studied for a variety of indications, including vaccines, topical anesthesia, skin disorders, cystic fibrosis, oral diseases, diabetes, osteoporosis, CNS, and more.[2]

Importantly, the field has witnessed a significant shift from conceptual development to clinical trials. An increasing number of companies are advancing their microneedle technologies into preclinical and early clinical stages, generating valuable data on efficacy, safety, and patient acceptability. This progression is crucial for validating the technology and paving the way for broader adoption.

The potential of microneedle technology has not gone unnoticed by funding bodies and government entities, which have made substantial investments in the space in recent years. These investments are catalyzing advancements through various stages of clinical development, reflecting growing recognition of the technology's potential to address global health challenges. Possibilities include bringing vaccines to more remote areas, increas-



A production line manufactures microneedle array patches.

ing national stockpiles to bolster preparedness for future pandemics, and improving the ease of vaccine administration.

WHY MICRONEEDLES & WHY NOW?

MAPs represent a significant leap forward in patient-centric drug delivery. The benefits from a patient perspective are clear and compelling. Microneedle patches offer a simple, intuitive application process that could potentially be done at home, possibly eliminating the need for healthcare provider administration. This potential for self-application not only increases convenience but could also address the issue of needle phobia.1 Patient preference surrounding administration is driving design decisions in the industry, with developers focusing on creating patches that are not only effective, but also user-friendly and minimally invasive. The potential for at-home administration also opens new possibilities for improving medication adherence and reducing the burden on healthcare systems.

From a clinical standpoint, intradermal delivery via microneedle patches offers several advantages. The rapid onset of action due to quick absorption into the bloodstream makes this method particularly attractive for certain therapeutics in which speed is crucial.[3] For vaccines, delivery to the dermis, rich in antigen-presenting cells, could potentially enhance efficacy and even allow for dose-sparing strategies.[4]

Perhaps one of the most transformative aspects of MAP technology is the potential for room temperature stability.[5] This characteristic could revolutionize the supply chain for many therapeutics, particularly vaccines. The ability to transport and store these products without stringent cold chain requirements addresses one of the most significant challenges in global health: the "last mile" problem in vaccine distribution.

This not only improves access, but also has significant environmental and economic benefits, reducing the carbon footprint and costs associated with maintaining cold chains.

ADDRESSING KEY CHALLENGES IN MICRONEEDLE MANUFACTURING

The benefits of microneedles are evident and as the field progresses, it's becoming increasingly clear that the next critical step is not just further innovation, but the ability to manufacture these designs at scale to take advantage of the potential for broad-reaching positive effects. Companies entering clinical development now face the challenge of navigating GMP clinical manufacturing and planning for eventual commercial production. An ability to navigate challenges in manufacturing is emerging as a key differentiator in bringing microneedle products to market.

COMPLEXITY ACROSS MANUFACTURING STAGES

The manufacturing process for microneedles is inherently complex, involving multiple steps that each require precise control:

Material Selection: The choice of materials for microneedle fabrication is critical, as it affects not only the mechanical properties of the needles but also their biocompatibility and drug release characteristics.

Microneedle Fabrication: This typically involves micro-molding processes that require high precision to consistently produce needles with the desired geometry and sharpness.

Drug Formulation: The drug must be formulated in a way that is compatible with the microneedle material and allows for efficient loading and release.

A worker adjusts parameters for microneedle array patch production.

Drug Loading: Depending on the microneedle type, this could involve coating processes, incorporation into dissolving materials, or loading into hollow needles.

Patch Assembly: The microneedles must be integrated with a backing layer and potentially other components to form the final patch.

Packaging: The packaging must protect the delicate microneedle structures and maintain product stability.

Each of these steps presents its own set of challenges when scaling up to commercial production. For instance, maintaining consistent needle geometry and drug loading across large batches requires highly controlled processes and sophisticated quality control measures.

Moreover, the interdependence of these steps adds another layer of complexity. Changes in one part of the process can have ripple effects throughout the entire manufacturing chain. This underscores the importance of considering manufacturability from the earliest stages of product design.

OVERCOMING DOSAGE LIMITATIONS

One of the primary challenges facing MAP technology is the limitation on the amount of drug that can be delivered in a single application. This constraint has historically restricted the scope of suitable drug candidates primarily to very potent substances, such as hormones and vaccines. However, recent research has made significant strides in optimizing delivery to overcome this hurdle.

Optimizing MAPs for delivering larger doses consistently requires careful consideration of several critical elements:

Needle Height: The height of the microneedles is a key factor in determining penetration depth and drug payload capacity;[1] while taller needles can potentially carry more medication, this must be weighed against user comfort and the risk of encountering pain receptors or blood vessels.

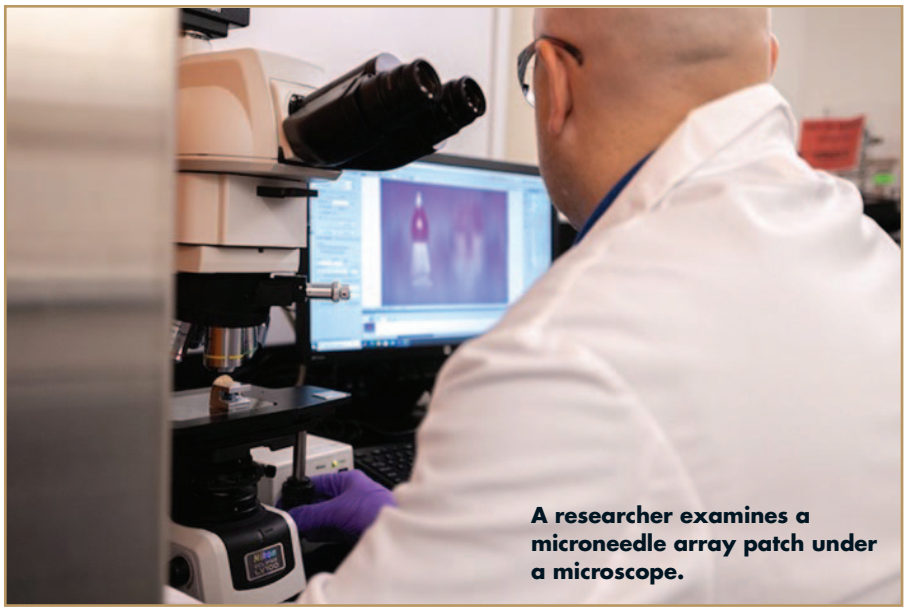
Microneedle Density: Increasing the quantity of microneedles on a single array can allow for a higher total dose delivery; however, this must be balanced with manufacturing feasibility and the potential for reduced penetration effectiveness due to force distribution across too many points, known as the "bed of nails" phenomenon.

Patch Dimensions & Layout: The overall size of the patch and the spacing between individual microneedles can impact both the total drug capacity and the uniformity of delivery; while larger patches can accommodate more needles or taller needles, they may be less user-friendly.[6,7]

Advanced coating techniques and formulation strategies are also being developed to maximize drug loading while ensuring rapid dissolution upon application.

Another crucial element for coated MAPs is the fine-tuning of droplet dimensions and placement on the microneedles. While larger droplets have the potential to carry larger drug doses, they may compromise the microneedle's skin penetration efficacy. Research has shown that smaller droplets situated near the microneedle tips tend to achieve higher delivery efficiency, as they are more likely to be completely inserted into the dermis. The specific location of the droplet on the microneedle can also impact both the speed of drug release and the skin depth at which the medication is administered.

These advancements are crucial for the path to commercialization. As the technology demonstrates the ability to deliver larger doses consistently, it expands possibilities for a wider range of therapeutics. This makes MAPs more attractive for pharmaceutical companies considering investment in this delivery method, potentially accelerating the journey from lab to market.



A researcher examines a microneedle array patch under a microscope.

BRIDGING THE GAP FROM LAB TO MARKET

As MAP technology progresses from early-stage development to clinical trials, the importance of GMP manufacturing capabilities becomes paramount. The ability to produce microneedle patches consistently at scale, while adhering to stringent quality standards, is as critical as the initial innovation itself.

Strategies for scaling up production involve careful consideration of material selection, manufacturing processes, and quality control measures. Injection molding has emerged as a preferred method for large-scale production of microneedle arrays due to its ability to produce complex geometries with high repeatability.[8] However, achieving consistent microneedle production at scale requires careful optimization of molding parameters and tooling.

Addressing regulatory considerations early in the development process is crucial. While specific guidelines for MAP products are still evolving, developers must anticipate requirements for sterility, bioburden control, and product stability. Early engagement with regulatory bodies and participation in industry working groups can help shape a clear path to approval.

COLLABORATION IN THE MICRONEEDLE SPACE

The complex nature of MAP development necessitates a collaborative approach. Partnerships between innovative biotech companies, academic institutions, and experienced manufacturers are becoming increasingly common and valuable. These collaborations bring together cutting-edge research with practical manufacturing expertise, accelerating the path to commercialization.

CDMOs are playing a crucial role in filling the manufacturing gap. With their expertise in GMP production and scale-up strategies, CDMOs are helping earlystage companies navigate the challenging transition to clinical, and eventually commercial, manufacturing. This support is critical for minimizing risks associated with the technology and attracting the investment needed for late-stage clinical trials.

Industry-wide collaboration and knowledge sharing are also gaining momentum. Working groups involving developers, manufacturers, and regulatory consultants are collaborating to establish best practices and address common challenges. This collective approach is helping to advance the field as a whole, creating a more robust ecosystem for microneedle patch development and commercialization.

TOWARD A HOLISTIC, FORWARD-THINKING APPROACH

Successful commercialization of MAP technology requires a holistic, IND-enabling mindset from the earliest stages of development. This approach integrates end-user needs, manufacturing scalability, and regulatory considerations into the initial design process, rather than addressing these factors as afterthoughts.

Integrating end-user needs into early-stage design ensures that the final product will meet real-world requirements. This includes considerations such as ease of application, patient comfort, and compatibility with various therapeutic agents. By prioritizing these factors from the start, developers can create MAPs that are not only technically impressive but also practically viable in clinical settings.

Considering manufacturing scalability from the outset is crucial for smooth progression through clinical trials and eventual commercialization. This involves selecting materials and designs that are amenable to large-scale production, and developing processes that can be reliably scaled up while maintaining product quality and consistency. Early collaboration with manufacturing experts can provide valuable insights into potential challenges and solutions.

Adopting this holistic strategy can significantly accelerate the path to market-ready products. It allows for more streamlined progression through clinical trials, smoother scaling of manufacturing processes, and more efficient navigation of regulatory pathways. By anticipating and planning for these challenges, companies can potentially bring their MAP products to market faster and with greater success. ◆

REFERENCES

1. Avcil, M., and Çelik, A. Microneedles in Drug Delivery: Progress and Challenges. Micromachines (Basel). 2021;12(11):1321. doi:10.3390/mi12111321.
2. ClinicalTrials.gov. Accessed May 17, 2023. www.clinicaltrials.gov.
3. Jung, J.H., and Jin, S.G. Microneedle for transdermal drug delivery: current trends and fabrication. J Pharm Investig. 2021;51(5):503-517. doi:10.1007/s40005-021-00512-4.
4. Ameri, M., Lewis, H., and Nguyen, J. Immunogenicity and safety of inactivated Influenza Split-Virion vaccine administered via a transdermal micro needle system. J Vaccines Immunol 2021;7.1, 41-48. doi:10.17352/jvi.000046.
5. Kim, Y.C., Park, J.H., and Prausnitz, M.R. Microneedles for drug and vaccine delivery. Adv Drug Deliv Rev. 2012;64(14):1547-1568. doi:10.1016/j.addr.2012.04.005.
6. Waghule, T., Singhvi, G., Dubey, S.K., et al. Microneedles: A smart approach and increasing potential for transdermal drug delivery system. Biomed Pharmacother. 2019;109:1249-1258. doi:10.1016/j.biopha.2018.10.078.
7. Loizidou, E.Z., Inoue, N.T., Ashton-Barnett, J., et al. Evaluation of geometrical effects of microneedles on skin penetration by CT scan and finite element analysis. Eur J Pharm Biopharm. 2016;107:1-6. doi:10.1016/j.ejpb.2016.06.023.
8. Mizuno, Y., Takasawa, K., Hanada, T., et al. Fabrication of novel-shaped microneedles to overcome the disadvantages of solid microneedles for the transdermal delivery of insulin. Biomed Microdevices. 2021;23(3):38. doi:10.1007/s10544-021-00576-x.

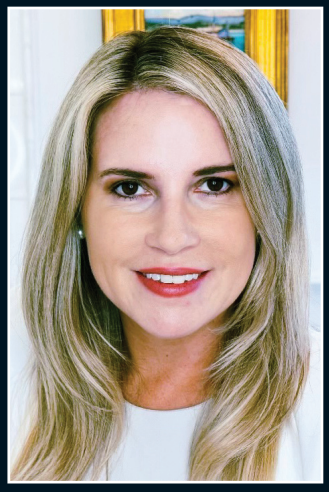
BIOGRAPHY

Andrew Riso serves as the Vice President, Dermal Delivery and Licensing at Kindeva Drug Delivery, where he leverages over 10 years of expertise in strategic planning, financing, market research, and commercial analysis within the biotech and drug delivery industries.

Drug Development
EXECUTIVE

RESILIENCE

Resilience Rising: Advancing Therapies That Transform Lives



Susan Billings, PhD

Chief Commercial Officer

Resilience

Resilience is poised to make an impact in biopharmaceutical manufacturing, addressing complex challenges in the development and manufacturing of life-saving and life-sustaining drugs. The company remains deeply committed to building a more resilient future, partnering with its customers to help bring transformative medicines to patients. *Drug Development & Delivery* recently interviewed Dr. Susan Billings, Chief Commercial Officer of Resilience. In this interview, she discusses pressing issues in the CDMO space, the opportunities driving innovation, and how Resilience is shaping the future of drug substance and drug product manufacturing. Having spent over a decade in the CDMO industry before a 2-year pivot to a TechBio startup, she is excited to return to the sector, bringing a renewed focus on building and growing Resilience's business.

Q: How has Resilience adapted to a changing market landscape since its founding in 2020?

A: Resilience was founded in 2020 with a bold mission: to ensure uninterrupted access to essential medicines, even in the face of challenges like those experienced during the pandemic. At a time when global supply chains were disrupted and critical raw materials and intermediates became scarce, Resilience recognized the need for a new approach to biomanufacturing that prioritized resilience, innovation, and patient access.

From the outset, we were fortunate to be well-funded, allowing us to thoughtfully and strategically invest in areas where we could make the greatest impact. This foundation enabled us to focus on technology-driven solutions and the advancement of biomanufacturing in critical areas such as viral vaccines, biologics, cell and gene therapy. For example, our facility in Allston, MA, has been reconfigured and optimized – with continuous manufacturing and several modular single use reactors to support early clinical through commercial drug substance biologics to further

strengthen our market position to meet growing industry demands and proximally located in one of the largest life science ecosystems in the world.

Over the past 4.5 years, we've continued to evolve, leveraging cutting-edge technologies and building capabilities that align with the industry's most pressing needs. While the pandemic heightened awareness of supply chain vulnerabilities, our efforts have remained steadfast: to provide access to medicines and ensure that patients receive the therapies they depend on without disruption. This commitment to innovation and strategic focus has positioned Resilience as a trusted partner in addressing both current and future challenges in the biopharma landscape, notably for the development and manufacturing of cell and gene therapies as well as other large molecule biologics.

Q: How does Resilience's name influence its mission and approach to partnering with clients?

A: Our name, Resilience, embodies exactly who we are and what we stand for. Born during one of the most challenging periods of our time, we entered the market amidst a global pandemic, only to face a rapidly shifting geopolitical and funding landscape that tested the entire industry. Yet, true to our name, we have adapted, persevered, and emerged stronger. We are dedicated to delivering innovative biomanufacturing solutions and transforming challenges into opportunities for growth and impact.

Q: Where do you see the greatest opportunity in the industry? In what areas is Resilience investing?

A: One of the greatest opportunities in the industry today remains the plight to combat cancer. This pursuit unites R&D and manufacturing organizations across all segments, including large pharma, mid-market biotech, emerging start-ups, CDMOs, and service providers. The shared passion to better understand the complex biology of cancer, develop therapies, and provide manufacturing options that can either extend life for late-stage patients or potentially provide life-changing cures drives incredible motivation to continue innovating. At Resilience, we remain committed to investing in and advancing cell therapy manufacturing with recent innovations, such as our DAR-T offering, that streamline vein-to-vein timelines of two weeks or less, reducing overall cycle times for autologous CAR-T cell therapies, ideal for treating B-cell malignancies, solid tumors, and auto-immune disorders. Additionally, we are investing in the development of another platform to shorten biomanufacturing release testing timelines, delivering realized benefits for overall cell therapy production.

Another significant opportunity in the industry is the growing momentum around GLP-1 therapeutics, which have expanded from their initial use in diabetes management to address obesity, weight loss, and even conditions like sleep apnea. This evolution has created tremendous potential for service providers and CDMOs to support the increasing demand for injectable products in this space. At Resilience, we have and will continue to prioritize investments in aseptic drug product formulation and manufacturing to become one of the fastest growing providers in the world for injectable products.

Staying ahead of industry trends is critical for any CDMO to succeed, but especially for a newer company like Resilience. As such, we have strategically chosen to invest in areas where we can deliver the most value to our clients and their patients. While the market landscape for certain modalities, such as gene therapy, has shifted, we've used these changes as opportunities to reassess priorities and focus on technologies and capabilities that align with current and future demands, particularly in autologous cell therapy and aseptic drug product manufacturing.

Q: What are companies looking for in a CDMO? What sets Resilience apart from other CDMOs?

A: Companies are seeking a trusted partner that can provide high quality, right first time delivery of products and services without compromising regulatory compliance. Resilience distinguishes itself in this area by acquiring facilities built to the highest industry standards, ensuring quality assurance and regulatory integrity that mitigate risks for our partners' IND filings and clinical trial timelines. Innovators are seeking a company with robust quality procedures and regulatory experience that safeguards their BLA filings and overall program success.

Resilience is more than a CDMO – we are a partner in innovation. While many traditional CDMOs adhere to legacy processes, Resilience was designed to challenge the status quo. Our digital and technology-first mindset, including advanced automation and industry leading equipment, drives efficiency for our clients, without compromising quality or regulatory compliance. Additionally, our 4.5-year-old roots are unique:

we've combined the energy of a new company with the proven expertise of people and facilities acquired from leading pharmaceutical and contract manufacturing organizations. This blend allows us to innovate and respond to our clients' needs rapidly while maintaining the highest standards of quality and reliability.

Q: Where are the biggest hurdles in process or technology, and is Resilience doing anything to address them?

A: The biomanufacturing industry faces significant challenges in the production of cell and gene therapies. For autologous cell therapies, one of the most pressing hurdles is the incredibly short manufacturing timeline required for a vein-to-vein process. Personalized therapies demand highly customized production, precise coordination, and strict quality control, all within a matter of days. This complexity not only impacts scalability but also creates substantial cost pressures for innovators, making it challenging to bring these therapies to a broader patient population.

Resilience has focused on addressing these challenges with solutions designed to improve efficiency, scalability, and cost-effectiveness. For cell therapy, our recently launched DAR-T platform exemplifies this approach by dramatically reducing manufacturing timelines for CAR-T therapies from 7–14 days to as little as 3 days. This process not only accelerates delivery to patients but also enhances the quality of the cells, yielding younger and more potent phenotypes that improve clinical outcomes. For our partners, the platform also reduces labor and material costs, making these therapies more accessible and scalable.

We take great pride in our ability to overcome one of the challenges in cell therapy manufacturing: meeting the critical turnaround time required to deliver these life-saving treatments to patients. By focusing on innovative solutions like our DAR-T platform, we're not only streamlining the process but also ensuring that therapies reach patients faster without compromising quality.

Q: With the changes that Resilience has experienced over the past 6 months, where do you see the company in 2 years?

A: In two years, I see Resilience as a recognized CDMO leader in biomanufacturing, delivering comprehensive end-to-end solutions from discovery through commercialization. We are reshaping our network to be well-positioned to meet growing demand in cell therapy, drug substance biologics, and sterile fill/finish for injectable products.

We're actively exploring opportunities to enhance our capabilities in complementary areas that support our downstream expertise in manufacturing and commercialization. This includes expanding our offerings for biologics and cell therapies, such as CAR-T and other cell types, while optimizing manufacturing processes to deliver sustainable, scalable, high-quality solutions. We are also prioritizing investments in expanding our aseptic fill/finish capacity to address the increasing demand for injectable products, ensuring we can meet the needs of our partners at every stage of their programs.

By strategically 'rightsizing' our network and refining our capabilities, Resilience is positioned to become the best version it can be with an agile, focused, and innovative mission as an industry leader in biomanufacturing. These efforts are guided by a clear roadmap that prioritizes quality, scalability, and sustainability, enabling us to help innovators navigate the complexities of biomanufacturing and deliver life-saving therapies to patients with greater speed and efficiency.

Our journey as a company has been one of adaptation and perseverance, staying true to our name and mission. Resilience has faced market and industry challenges head-on, emerging stronger and more focused on delivering value to our partners and the patients they serve. As we continue to grow, we are committed to advancing the capabilities of biomanufacturing, ensuring access to life-saving therapies, and setting the standard for excellence in the industry. ◆

CELL SEPARATION TECHNOLOGY

Breaking Down Barriers to Unlock a New Era of Cell Therapy

By: Liping Yu, PhD

INTRODUCTION

Cell therapy has, for many years, held the promise of revolutionizing the treatment of cancer and other diseases by harnessing the power of the patient's own immune system and providing an effective last-resort cure where other treatments have failed. However, until recently, high production costs and inefficient processes have hampered the field. Now, recent advancements are helping to remove these barriers to R&D and are ultimately making treatments, such as CAR-T, CAR NK, and stem cell therapies, more accessible than ever to patients. CAR-T cell immunotherapy, in particular, has shown promising results in treating blood cancers – including multiple myeloma and certain forms of leukemia and lymphoma – whereby T cells are first extracted from a patient's blood, and then genetically modified in a laboratory to express a chimeric antigen receptor (CAR).[1] Once infused back into the patient, these modified T cells target the cancer cells expressing the specific protein recognized by the CAR. This approach to treatment helps to minimize the damage to normal, non-cancerous cells, causing fewer side effects and leading to more effective treatment.

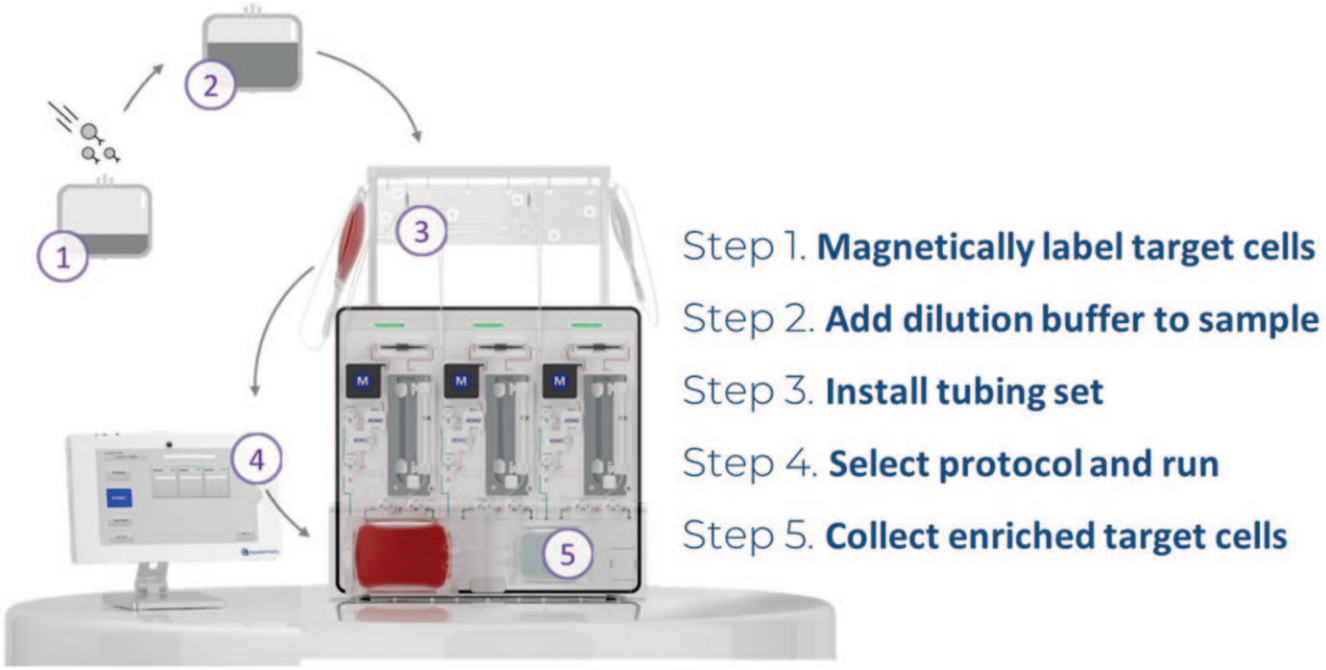
POINT-OF-CARE AUTOLOGOUS CELL THERAPY MANUFACTURING

Current CAR-T cell production for these therapies is largely centralized, with healthcare centers sending patient samples to specialized manufacturers, but the situation is far from ideal. Unfortunately, transporting cells and final products between healthcare providers and producers requires cold chain storage, incurring high logistics costs. The wait time between initial cell harvest and the receipt of the therapy back at the hospital can also be in the order of several months, delaying the onset of critical treatment. Decentralized manufacture of autologous CAR-T cells closer to the point of patient need – for instance in a hospital laboratory – would address some of these challenges, starting with avoiding long-distance transportation and the associated expenditure. The turnaround time from cell harvesting to the administration of therapy would also be much shorter, potentially as little as 3 days, enabling earlier and more effective treatment. There is therefore a trend in both North America and Europe for larger medical institutions to manufacture their own cell therapy products on site according to good manufacturing practices (GMP) instead of outsourcing production. Regulatory agencies are also recognizing the difference between cell therapy and conventional drug products, supporting the development of novel advanced therapies by offering healthcare institutions that satisfy rigorous GMP and quality control requirements an exemption and enabling easier access to cell therapy for patients.[2]

STREAMLINING CAR-T CELL MANUFACTURE

The actual process of traditional CAR-T cell manufacturing itself can take up to 12 days from initial harvest, including T cell isolation and activation, gene transduction and *ex vivo* expansion. This expansion process is extremely resource intensive and costly, and also exhausts CAR-T cells, causing them to lose their potency and efficacy as a cell therapy. Recent studies have shown that the *ex vivo* expansion process is, in fact, not strictly necessary in many

FIGURE 1



The MARS® Bar platform from Applied Cells uses column-free sterile fluidic technology and offers a convenient and affordable method for isolating T cells in a closed system.

cases, as CAR-T cells are capable of proliferating by themselves in the body.[3,4] Direct infusion of CAR-T cells into the bloodstream would therefore preserve their potency and allow therapies to be delivered to patients sooner. Bypassing the lengthy expansion phase would also significantly reduce overall manufacturing costs, encouraging wider production and adoption of cell therapies. For these reasons, many major biopharma players and large medical institutions are now implementing rapid manufacturing processes that take as little as 3 days and are more cost effective than previous production methods.[5,6]

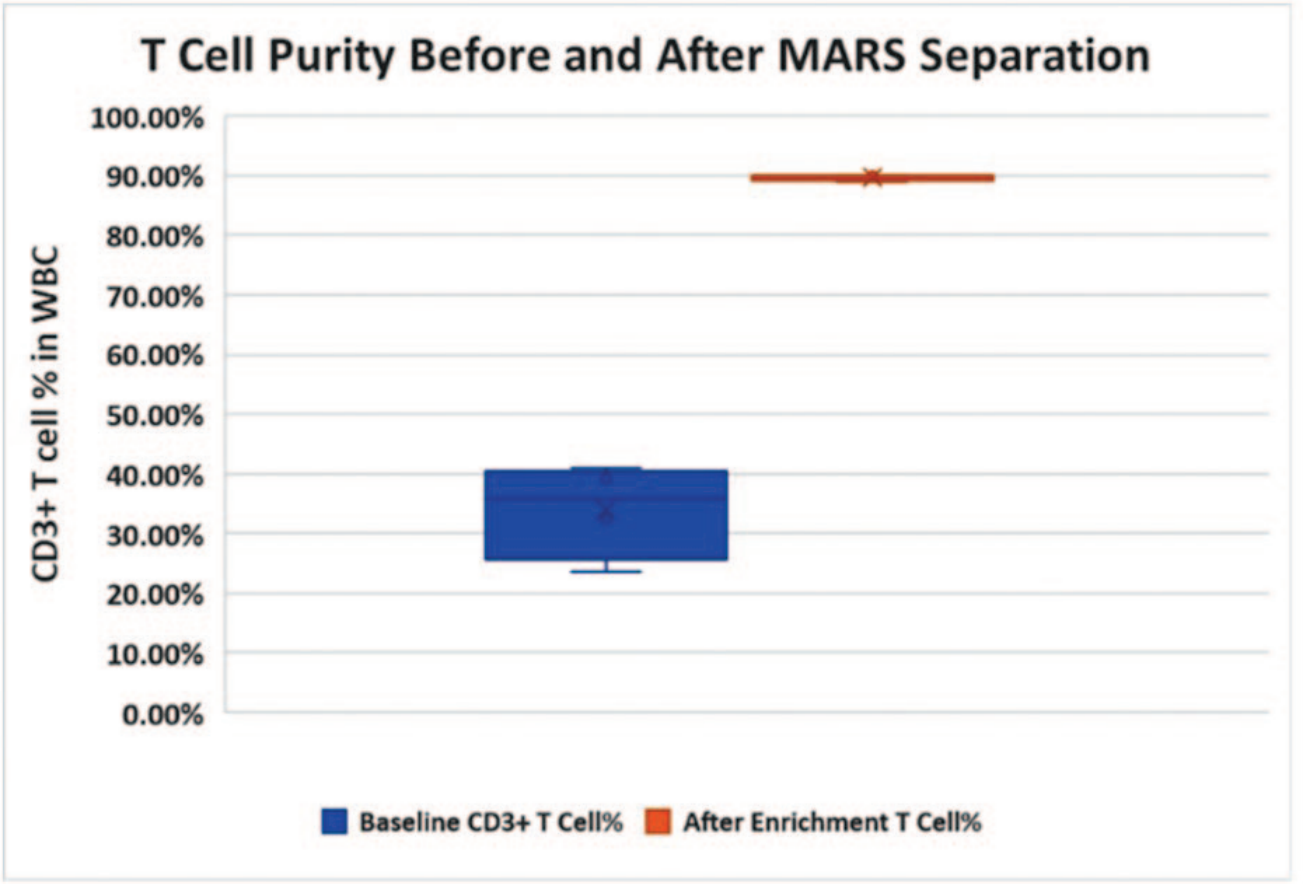
STRIKING THE RIGHT BALANCE BETWEEN CARE AND COST

Outside of manufacturing, the overall cost of treatment to a healthcare provider is largely wrapped up in the resources required for long-term patient care. The US FDA requires that patients are pre-treated and well monitored before a full dose of cell therapy is administered in order to avoid any adverse effects such as cytokine release syndrome. This condition is severe and usually leads to prolonged stays in the intensive care unit (ICU), significantly increasing overhead and resource costs for the hospital. In some trials, lower doses of more potent CAR-T cells have been shown to elicit a far milder form of cytokine release syndrome, with only a very small percentage of patients suffering from the condition in comparison to those treated with higher doses.[7] Using smaller doses of more potent CAR-T cells – produced through rapid manufacturing processes and administered directly – could help to prevent ICU admissions and shorten hospital stays. This in turn would contribute to reducing the financial burden of treatment to healthcare providers.[8]

OVERCOMING HURDLES IN CELL SEPARATION

There are understandably still some challenges that must be overcome to ease the transfer of cell therapy production from specialized to healthcare facilities. T cell separation is a critical upstream process within CAR-T cell manufacturing and has a significant impact on the quality of the cells produced, subsequently affecting the ultimate success of the therapy. Separating T cells from blood with adequate levels of purity, viability, and concentration can be difficult, with the technical limitations of conventional cell separation techniques – such as density gradient centrifugation, column-based magnetic cell separation, and fluorescent activated cell sorting (FACS) – significantly hindering research capabilities. When employing these methods, multiple platforms are typically needed for each sample preparation, extraction, engineering and culture stage, all

FIGURE 2



T cells are enriched up to 90% percent purity on average after separation on the MARS Bar platform.

with their own single-use components and costly reagents. These set-ups are therefore not only expensive for researchers and manufacturers, but also occupy a lot of space and require constant manual input. In addition, current cell separation and enrichment protocols often result in suboptimal purity, yield, and cell viability, potentially limiting patient access to state-of-the-art drugs. These shortfalls are driving researchers and manufacturers in the biopharma and healthcare spaces to improve the efficiency of cell separation processes for enhanced purity and yield.

Powerful automated solutions now exist for rapid, column-free immunomagnetic cell separation (Figure 1). These platforms use matrix-free magnetic technology to reduce dead volume and cell trapping, isolating cells with high purity and recovery rates (Figure 2). This method also does not use centrifugation, treating cells gently to preserve their viability and physiology for downstream functional studies. Systems based on this methodology are compatible with a variety of input sample types, including peripheral blood, bone marrow, and apheresis products, and do not require cell washing before or after labelling, greatly simplifying the cell separation workflow. Features such as automated three-pass cell enrichment also confer consistent separation between runs, making it possible to process billions of cells in a single closed system operation. This capacity increases throughput and enables users to avoid slow and laborious manual methods, allowing them to just walk away and get on with other tasks. The addition of options, including sterilizable, reusable fluidics along with economical, GMP-compliant consumables, is also helping to reduce per sample running costs and contribute to cost-effective R&D and scale-up.

The development of compact platforms based on this technology that can easily be adapted for use in both research and manufacture, where the same protocols can be applied across all development stages, is effectively streamlining and standardizing the transition from R&D to commercial and decentralized production. This avoids the need to purchase extra platforms for scale-up and allows manufacturers in biopharma and healthcare to circumvent additional process development after initial set-up and optimization.

AN ENCOURAGING OUTLOOK FOR PERSONALIZED MEDICINE

Autologous CAR-T cell therapies have already been successful in treating hematological cancers, accelerating research into their applications for a broad range of other disease areas. In fact, multiple clinical trials investigating the efficacy of these immunotherapies for treating autoimmune diseases, such as systemic lupus erythematosus, and hereditary disorders including cystic fibrosis, are currently underway, and are already showing promising results.[9] Revolutionary cell separation technologies are crucial for enabling these rapid advancements, and will continue to play a growing role in establishing the decentralized, rapid, and cost-effective large-scale manufacture of potentially life-saving cell-based drugs well into the future.

*For research use only. Not for use in therapeutic or diagnostic procedures. ◆

BIOGRAPHY

Dr. Liping Yu is VP of Applications at Applied Cells, overseeing application development, providing customers with complete solutions by integrating reagent, hardware, and software on the MARS platform. She earned her PhD from Carnegie Mellon University in 2006 and then undertook postdoc training and career development at Beckton Dickinson. She is an experienced team leader with a track record of strategic planning and customer engagement, having overcome significant business and technical challenges to deliver a successful product from concept to production, and led a versatile team spanning across the company's organizational boundaries through technology development. She has additionally established a large number of close and collaborative relationships with academic and industrial partners.

REFERENCES

1. National Cancer Institute. CAR T Cells: Engineering Patients' Immune Cells to Treat Their Cancers. National Institute of Health .
2. Giorgioni L, Ambrosone A, Cometa MF, Salvati AL, Magrelli A. CAR-T State of the Art and Future Challenges, A Regulatory Perspective. Int J Mol Sci. 2023;24(14):11803. doi:10.3390/ijms241411803
3. Ghassemi S, Nunez-Cruz S, O'Connor RS, et al. Reducing Ex Vivo Culture Improves the Antileukemic Activity of Chimeric Antigen Receptor (CAR) T Cells. Cancer Immunol Res. 2018;6(9):1100-1109. doi:10.1158/2326-6066.CIR-17-0405
4. Ghassemi S, Durgin JS, Nunez-Cruz S, et al. Rapid manufacturing of non-activated potent CAR T cells. Nat Biomed Eng. 2022;6(2):118-128. doi:10.1038/s41551-021-00842-6
5. Yang J, He J, Zhang X, et al. Next-day manufacture of a novel anti-CD19 CAR-T therapy for B-cell acute lymphoblastic leukemia: first-in-human clinical study. Blood Cancer J. 2022;12(7):104. doi:10.1038/s41408-022-00694-6
6. Dickinson MJ, Barba P, Jäger U, et al. A Novel Autologous CAR-T Therapy, YTB323, with Preserved T-cell Stemness Shows Enhanced CAR T-cell Efficacy in Preclinical and Early Clinical Development. Cancer Discov. 2023;13(9):1982-1997. doi:10.1158/2159-8290.CD-22-1276
7. Ayala Ceja M, Khericha M, Harris CM, Puig-Saus C, Chen YY. CAR-T cell manufacturing: Major process parameters and next-generation strategies. Journal of Experimental Medicine. 2024;221(2). doi:10.1084/jem.20230903
8. Ayala Ceja M, Khericha M, Harris CM, Puig-Saus C, Chen YY. CAR-T cell manufacturing: Major process parameters and next-generation strategies. Journal of Experimental Medicine. 2024;221(2). doi:10.1084/jem.20230903
9. Blache U, Tretbar S, Koehl U, Mougiakakos D, Fricke S. CAR T cells for treating autoimmune diseases. RMD Open. 2023;9(4):e002907. doi:10.1136/rmdopen-2022-002907.

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DRUG DEVELOPMENT

What is Formulation Development & Why is it Important?

By: Rob Holgate, PhD, and Nicola Watts, PhD

INTRODUCTION

Formulation Development is fundamentally about understanding how a drug's properties, such as chemical structure, solubility, stability, and bioavailability, change as a result of how it is formulated. The process, although often overshadowed by the clinical aspects of drug development, plays a critical role in the development and manufacture of stable, safe, and effective medications. It is, in essence, where science meets practicality. This process involves a delicate balance of scientific rigor and practical application, and not only requires a profound understanding of the drug's properties, but also the ability to navigate the many challenges of delivering the drug in an effective and patient-centric manner.

WHEN DOES FORMULATION DEVELOPMENT TAKE PLACE?

Biopharmaceutical formulation development can be applied in tandem with Cell Line Development, later once the manufacturing process has been developed, or as part of clinical life-cycle product management. However, in a constantly evolving discovery and development landscape, there is a continual push to bring key activities forward, do more with less, and progress multiple candidates in parallel as far as possible. While there are clearly some aspects that cannot be performed at an earlier stage (eg, activities that require information derived from Phase 1/2 clinical trials used to support dosage for future clinical phases), there are several aspects that can be considered early on, and that should form part of lead candidate selection criteria. Therefore, formulation development represents a spectrum of activities spanning from late discovery/early development, all the way through to Phase 3.

A PROACTIVE APPROACH TO FORMULATION DEVELOPMENT

Effective drug formulation hinges on early detection of potential drug instabilities. At Abzena, we apply a series of rigorous stress tests designed to assess how well a drug will hold up during the manufacturing process, as well as its stability on long-term storage. Strategic decision-making, informed by the outcomes of these tests, guides developers in refining the formulation process. By proactively identifying formulation challenges early, potential setbacks in later stages of development can be avoided, which is essential for efficient and successful drug development and production.

A Best-Practice Formulation Strategy

The formulation of a biologic drug is a complex process that involves multiple stages, each playing a crucial role in ensuring the safety, efficacy, and manufacturability of the final product. This journey begins with a thorough understanding of the drug's physicochemical properties. Subsequent stages involve developing and refining the formulation to address any potential challenges, optimizing it for manufacturing, and conducting extensive stability testing.

The stages of biopharmaceutical drug formulation from ini-

tial analysis to final optimization include:

Stage 1: Developability assessment and manufacturing stress studies.
Stage 2: Pre-formulation.
Stage 3: Pre-manufacturing optimization.
Stage 4: Extended stability testing.
Stage 5: Freeze-thaw stability.

It is the first stage of formulation development that we will focus on for the remainder of this article to highlight the importance of this stage.

FORMULATION & DEVELOPABILITY

What is Developability?

Developability, simply put, is an overarching concept that describes the properties that predict the ease and likelihood with which a candidate molecule can be developed into a safe, effective, manufacturable, and marketable drug.

The Role of Developability Assessments

Performing an assessment to understand these developability properties is pivotal in the early stages of drug development as this serves not only to assess the viability of any given lead candidate but also, by utilizing a battery of assays early on, allows effective triaging and candidate selection from a larger panel of leads. These assessments aim to provide a comprehensive evaluation of a drug candidate's intrinsic characteristics ensuring they are amenable to development, scale-up and commercialization, and by focusing on critical biophysical properties, help identify potential roadblocks that could impede a drug's path from laboratory to market.

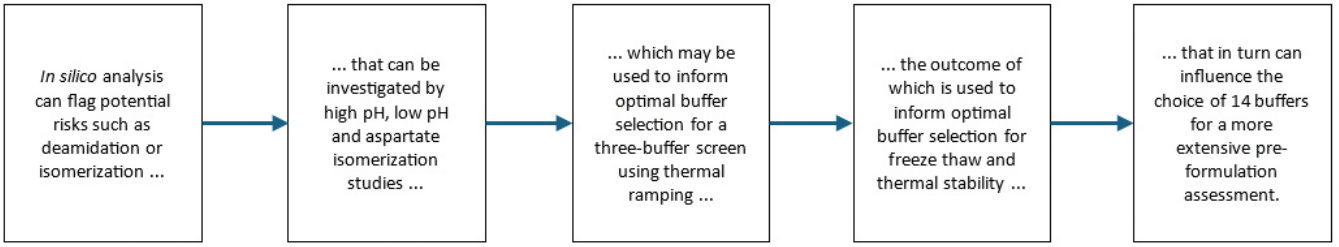
One of the key areas of focus for de-

TABLE 1

Study	Description	Relevance to Development
Freeze-thaw study	Assesses susceptibility to aggregation as a result of temperature cycling by performing multiple freeze-thaw cycles.	Critical for the development of the drug product as a frozen liquid or if used as a shipping condition.
Acidic pH stability study	Assesses the molecule's ability to withstand a low pH hold by subjecting the test sample to low pH stress (pH 3.5).	Vital to assess stability to viral inactivation conditions in DSP.
Basic pH stability study and forced deamidation	Assesses the molecule's susceptibility to deamidation events and identification of degradation pathways by subjecting the test sample to high pH stress (pH 9.0).	Useful in determining susceptibility of the drug product to high pH during unplanned pH excursions in DSP.
Thermal stress study	Assesses susceptibility to degradation using incubation at an elevated temperature.	Essential for assessment of sensitivity towards temperature excursions (e.g. prolonged hold at RT) and can be used as a predictor for long-term stability.
Oxidative stress study	Assesses methionine and tryptophan susceptibility to oxidation.	Used as a method to determine sensitivity towards oxidation which may occur from degradation of certain excipients over time or to oxygen ingress in sealed drug product vials.
Colloidal stability stress study	Assesses colloidal behaviour in a selected buffer and concentration.	Can be used as a predictor of general stability in solution and of higher concentrations.
Viscosity	Assesses sample viscosity.	Can be used to predict the viability of the drug product as a high concentration product for potential sub-Q administration.

Example developability studies.

FIGURE 1



Example Workflow

velopability assessment is stability as this directly impacts a biological drug's effectiveness and safety over time. To be viable as a potential candidate, a protein must maintain its colloidal stability, chemical integrity, and therapeutic potency not just during the manufacturing process and in final drug product, but also through long-term storage, shipping, and in-use handling. With a preference that molecules have a solution stability of at least 2 years, obtaining real-time stability data is extremely time-consuming. Consequently, at early stages of formulation development, properties are scrutinized through a series of accelerated stability stress studies that aim to mimic and predict how the drug will behave in real-world scenarios, ensuring that any potential issues can be addressed before significant investments are made.

Example studies may include:

- **Low pH stress study** - designed to mimic conditions encountered during the viral inactivation step as well as being a common manufacturing step to elute off protein A.
- **Freeze thaw study** - to test intrinsic stability towards freezing and thawing conditions which the drug may be subjected to if the final presentation is a frozen liquid.
- **Thermal stress study** - where a sample is stressed at a higher temp to mimic temperature excursions that can happen for example during transit where a cold-chain cannot be maintained.

From a holistic drug development perspective, the value of assessing developability is immeasurable. Developers can not only identify viable candidates by predicting potential manufacturing and scalability challenges early, they can also devise strategies to mitigate any downstream development risks and inform the final form of drug product for clinical evaluation. This reduces the likelihood of late-stage failures and significantly cuts down on development costs and time. As such, developability assessments represent a strategic tool that guides the decision-making process, ensuring that only the most promising drug candidates are advanced into the more costly and time-intensive phases of clinical trials. By applying these assessments, developers can prioritize and, if necessary, reallocate their resources to focus on candidates with the highest potential for success and market impact.

How to get the Most From a Developability Assessment?

Developability assessment should, at a minimum, investigate stability-associated parameters, including thermal, freeze thaw, and acidic stability. *In silico* evaluation may also identify additional risks, such as isomerization or deamidation sites that may require additional studies at this stage. Particular attention should be paid to risks that may lead to decreased drug potency/activity, with binding assays performed on stressed samples to understand the impact.

While these types of studies are considered fairly typical, there are nuances around how they can be performed and therefore the interpretation of the data and usefulness of information gained. As a simple example, there is a tendency for phosphate-buffered saline (PBS) to be used as the "default" buffer when screening large panels of monoclonal antibodies (mAbs) in earlier stages of discovery given the convenience of an off-the-shelf reagent. However, experience suggests PBS is not always an ideal buffer, and using it sometimes can lead to poor decision-making, especially if used at later stages of candidate selection.

One approach to enable better decision-making is to perform a limited three-buffer thermal ramping stability screen prior to stability studies, such as thermal stress and freeze thaw. In this approach, PBS (or the buffer the sample is provided in) together with a histidine pH 6 buffer containing pre-defined concentrations of NaCl or sucrose are recommended. As a starting point, this captures most elements

of a "good enough" buffer. Performing a thermal ramping assessment on multiple lead candidates in these three buffers aims to ensure that, when moving into the thermal stability and freeze thaw studies, no candidate is disadvantaged simply by being in the "wrong" buffer and thereby improves likelihood of selecting the best candidate. Additional information gained at this stage can also indicate a preference for NaCl or sucrose which can, in turn, be used to influence the panel of buffers and excipients used within the broader pre-formulation study.

The three-buffer screen previously described can be modified further based upon prior studies. By way of example, if an in-silico or bench assessment has identified a potential isomerization site, then it may be desirable to modify the buffer screen by making it slightly less acidic, eg, using a histidine buffer at pH 6.5 instead of 6.

As the high pH, low pH, and aspartate isomerization stress studies are generally formulation buffer-agnostic, they can be performed without the need for the buffer screen and additionally, can provide essential information to guide and inform downstream formulation as well as process development activities. For example, the low pH study may suggest a potential issue with using a low pH hold as part of the manufacturing process and may require modifications to the process, through using either a slightly increased pH (within viral inactivation constraints) or an alternative low pH buffer. Additionally, forced degradation assessments can elucidate pH-dependent behaviors that can help determine if changing the formulation to avoid one liability may inadvertently increase the risk of a new unwanted liability. For example, whether raising the pH to avoid Asp isomerization may in turn promote additional liabilities such as Asn deamidation. Keeping a close eye on binding affinities of a candidate post-stress can also mitigate against conditions, which may appear to be stabilizing and yet in reality render the molecule less potent.

Challenges of Bringing Formulation Development Forward

Formulation development studies can typically be very material intensive, and so one of the key limitations of earlier stage testing is material availability. In this regard, expression systems have developed enormously over the last 10+ years and the ability to obtain significant quantities of material at an acceptable cost and timeframe is continually improving, thus increasing the potential to screen more candidates.

However, as discussed earlier, biologics development itself is constantly evolving, with the continual challenge being of how to do more with less. One key area of focus is how to bring high concentration studies forward so they can be performed as part of the candidate triaging. Different approaches are being explored, including using high throughput/low material requirement platforms, such as the Uncle (Unchained Labs) or Prometheus Panta (Nanotemper) to determine the diffusion interaction parameter (kD) that has been reported to be a predictor of high concentration behavior. Other surrogate assays exist, such as AC-SINS (a method that monitors antibody self-association); however, these are more typically used to understand properties such as pharmacokinetics (PK). AC-SINS is typically performed in PBS and, as with stability studies, the necessity of screening self-association behavior in more relevant formulation conditions has been recognized. One such method is PS-SINS, an optimized method that enables profiling of mAbs in several formulation conditions, including the previously unfeasible histidine formulation, and suggests that the PS-SINS profiling data (beyond the single PBS condition) provide richer and more valuable information for early-stage antibody triaging.

Risks of Not Considering Formulation Development Early On

Neglecting early stage developability assessments and pre-formulation screening can lead to significant and often avoidable challenges. Numerous case studies across the pharmaceutical industry illustrate how insufficient early testing has resulted in major setbacks, for example, drugs that appeared promising in early biological assays have faltered during Phase 2 or 3 clinical trials because issues like poor stability or instability were not addressed upfront.

The financial and operational implications of these oversights are substantial. Development delays not only lead to additional costs associated with testing and reformulation but also extend the time to market, which can have significant competitive and financial repercussions. This in turn, can damage investor confidence when projects do not progress as anticipated, affecting a company's financial standing and its ability to secure future funding. Operationally, shifting the team's focus from advancing the development pipeline to troubleshooting and resolving formulation or stability issues, can impact not only the drug in question but also delay development of other molecules in the pipeline.

Therefore, investing in comprehensive early stage assessments is not merely a

technical necessity, but a strategic imperative that underpins the success of a company as it strives to develop new pharmaceuticals for patients in need. ◆

BIOGRAPHIES

Dr. Rob Holgate has over 25 years of experience in Drug Discovery and early stage Development. After earning his PhD in Molecular Medicine at UCL, he moved to The University of York as a post-doctoral researcher. He subsequently worked at Cambridge Antibody Technology before joining Antitope (now Abzena) in 2008 as a Research Manager, then leading Abzena's Discovery and Protein Engineering group. Now, as VP of Research and Innovation, he plays a key role working with clients to understand the challenges they may face during discovery and early development to help them develop safe and effective therapies.

Dr. Nicola Watts is a Principal Scientist in the Analytics Group at Abzena and has been with the company for over 3 years. She has a background in formulation spanning 8 years, during which she has worked on numerous projects involving formulation of mAb biosimilars, formulation of GLP-1 type peptides, co-formulations, high concentration subcutaneous products, high-throughput formulation strategies utilizing liquid handling robotics, and late-stage formulation activities, such as container/device compatibility. Previous to Abzena, she worked at Intertek Melbourn focussing on inhalation therapies for the treatment of conditions such as COPD. During this role, she also investigated novel strategies aimed at the successful nebulization of biologics for inhalation administration.

Drug Development
EXECUTIVE

Thomas Guldager

Vice President, Operations

Lifecore Biomedical

Lifecore Biomedical: Capacity to Keep Pace With Biologics Growth

With a 40+ year regulatory track record, Lifecore is a fully integrated CDMO with highly differentiated capabilities in the development, fill and finish of sterile injectable pharmaceuticals, including 20+ commercial products. *Drug Development & Delivery* recently interviewed Thomas Guldager, Vice President, Operations at Lifecore.

Mr. Guldager recently joined U.S.-based Lifecore Biomedical after leading manufacturing at Xellia Pharmaceuticals, a Danish API manufacturer and wholly owned subsidiary of Novo Holdings A/S. During his tenure, he also served as Director of Business Excellence and Director of Operational Excellence.

His career has also included a tenure as Chief Operating Officer of Vertanical, a Germany-based biopharmaceutical company, Supply Chain Controller for ReckittBenckiser, a British-Dutch multinational consumer goods company, and Finance Officer for GlaxoSmithKline.

Q: Many industry reports cite that biologics are a rapidly growing area of the pharmaceutical market. Does that hold true for injectable products?

A: Yes, in recent years the FDA approvals for injectables have been led by biologics. Although those numbers only represent the US market, we've seen an increase in the number of global opportunities related to biologics, and we expect that trend to continue.

"Many of the special considerations and modifications that need to be made in the process development and fill/finish of biologics are the same things we address for complex, small molecules. Every process is designed and built around the molecule, no matter the type."

Q: What biologic products can Lifecore support?

A: Our facility infrastructure and Quality Management System (QMS) can support a range of biologics including monoclonal antibodies (mAbs), therapeutic proteins, peptides including GLP-1s, mRNA/lipid nanoparticles, and others. Our QMS also incorporates requirements across product types and geographies, providing flexibility for specific customer needs.

In addition, our development team has prior industry experience in the biologics space and has been able to share knowledge to help Lifecore continue expanding within biologics.

Q: How is handling biologics similar to small molecules?

A: Biologics are more complex, and this complexity can add sensitivities that need to be understood and mitigated during production. However, in many ways, the fill/finish of a biologic is not unique. The manufacturing steps are virtually the same. All sterile injectable production requires stringent aseptic techniques to prevent contamination throughout manufacturing processes and environments.

Q: So, what is special about biologics from a development and fill/finish perspective?

A: Shear sensitivity is a major consideration. To preserve the critical structure-function relationship of biologic molecules, manufacturing equipment trains must be designed to minimize exposure to shear stress. In fill/finish activities, this involves special considerations for mixers and filling pumps. For example, peristaltic pumps are often preferred over rotary piston pumps because they cause less shear when operating.

A second major area is sterilization. Due to their nature, biologics must undergo sterile filtration as opposed to terminal sterilization. This can be challenging, especially since formulations with higher concentrations of biologics result in an increase in viscosity. Lifecore has proprietary technology that enables sterile filtration of high-viscosity formulations to address this challenge.

Also, biologic APIs are typically more expensive, so minimizing loss is important. When developing a manufacturing process, short distances between fill tanks and fillers are preferred. The amount of drug product used during development/engineering runs should be minimized as well.

That said, many of the sensitivities associated with biologics are also present with complex small molecules, i.e., light sensitivity, and time-out-of-refrigeration (TOR) constraints. As a producer of a variety of ophthalmic products which have requirements that can be stricter than biologics, such as particulate size limitations, Lifecore is used to adjusting for molecular sensitivity.

Q: What about from an analytical testing perspective?

A: Characterization of large molecules is more challenging, typically requiring the development of multiple analytical techniques to analyze structure, purity, and other physical and chemical characteristics. There is some overlap between commonly used equipment but, at times, we acquire different instruments to support biologics.

Q: Can Lifecore support biologics from a regulatory standpoint?

A: Among the types of products we handle, requirements for biologics and small molecules are similar. Lifecore is well-positioned to comply with biologic requirements due to our infrastructure and processes for other complex products. Plus, we have strong relationships with global regulatory bodies to help move customer products across the finish line.

Q: What capacity do you have to support the growing biologics market?

A: With the recent installation of our high-speed, 5-head isolator filler, we doubled our capacity to support all types of injectables in vials, syringes, and cartridges. Plus, this filler offers several benefits that are especially valuable for biologics, including optimization of filling parameters to reduce losses at start-up, during production, and at the end of a batch, as well as non-destructive, in process weight checks.

For those who haven't fully developed their platform, our pilot laboratory is well-equipped to produce engineering batches and pre-clinical study material. We also have on-site laboratories, an ICH stability program with a range of conditions that accommodate biologics, and in-house secondary packaging.

Q: What trends do you see related to biologics?

A: From a container perspective, we are seeing a need to move away from traditional vials early in the development cycle toward combination products that can support the use of large volume, wearable devices. Also, we see the application of technologies to increase dosage concentration while maintaining sub-cutaneous administration. Again, Lifecore is well-positioned to support these trends with our increased capacity, infrastructure, and capabilities.

"Many of the special considerations and modifications that need to be made in the process development and fill/finish of biologics are the same things we address for complex, small molecules. Every process is designed and built around the molecule, no matter the type." ◆

VACCINE DEVELOPMENT

Enhancing Pandemic Preparedness With Mosaic-8b Nanoparticles

By: Leonardo Magneschi, PhD

INTRODUCTION

Vaccines have long been pivotal tools in controlling infectious diseases, significantly decreasing the global disease burden by helping to prevent illness, reduce transmission, and protect vulnerable populations. Most importantly, immunization has saved countless lives over the years by preventing severe outcomes, particularly in diseases with high mortality rates, such as smallpox, measles, and tuberculosis. These benefits were brought sharply into focus during the recent COVID-19 pandemic, when the rapid development and distribution of vaccines played a significant role in mitigating the spread of the virus. Today, vaccine research is advancing further with the development of a broad-spectrum vaccine providing cross-reactive immunity against both current and future strains of sarbecoviruses. This innovative preventive treatment strategy has the potential to boost global resilience against future outbreaks.

ADDRESSING GAPS IN THE CURRENT VACCINE LANDSCAPE

The COVID-19 pandemic demonstrated the transformative power of vaccines in safeguarding global health. Despite over 7 million reported COVID-related deaths since January 2020 – a number that continues to increase daily – the rapid development and rollout of vaccines has saved countless lives.[1] Estimates suggest that COVID-19 vaccines prevented approximately 20 million deaths worldwide in their first year of availability alone.[2] Since then, they have helped to reduce the overall risk of death by as much as 57%, providing a critical line of defense against the virus's spread.[3] However, the natural tendency for viruses to mutate poses ongoing challenges, making it difficult for immunologists to keep pace.

An Evolving Challenge

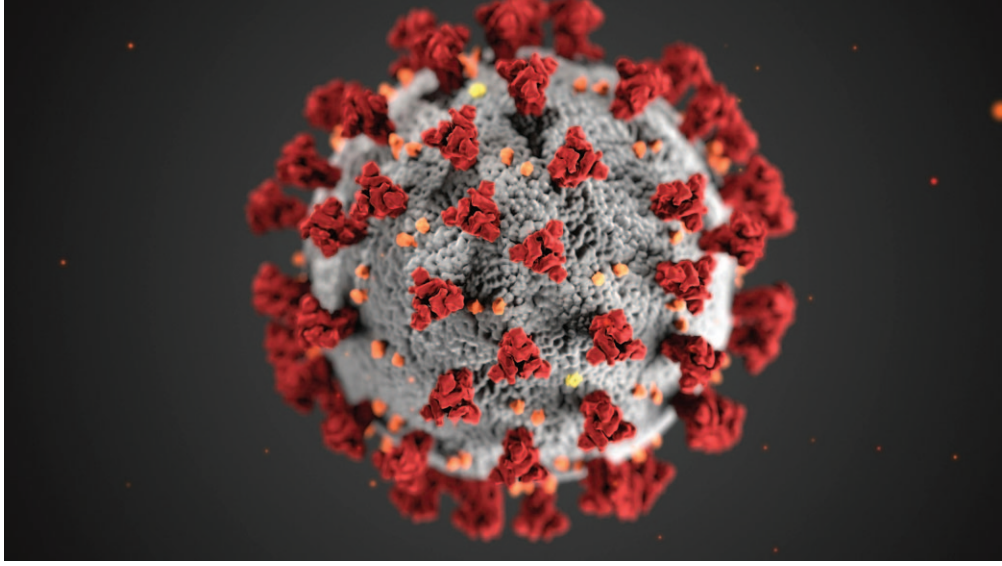
Most current COVID-19 vaccines work by presenting fragments of the SARS-CoV-2 spike protein to the body, allowing the immune system to recognize and fight off the virus. This mode of action proved highly effective during the initial vaccine rollout, leading to widespread immunity. However, RNA viruses like SARS-CoV-2 have a highly error-prone replication process and are therefore likely to have high mutation rates.[4] This results in the production of new viral strains with altered antigenic epitopes – regions on the surface of the virus that the immune system recognizes and targets. When these epitopes change, existing antibodies may not recognize or bind to the virus with the same affinity, reducing the immune system's ability to neutralize the virus and allowing it to evade a previously effective immune response. For instance, substitutions in the SARS-2 spike protein receptor-binding domains (RBDs) of the Omicron variant have reduced the efficacies of both vaccines and therapeutic monoclonal antibodies, leading to breakthrough infections in individuals previously immune to the original strain.[5,6] Continuing viral evolution may therefore mean that current vaccines struggle to provide sustained protection, as they were designed to target earlier versions of the virus.[7] This emphasizes the need for updated or alternative vaccine strategies that can generate neutralizing antibodies capable of effectively targeting emerging variants.

A Temporary Fix

At the peak of the COVID-19 pandemic, developing variant-specific boosters was a necessary approach to help extend protection against evolving viral strains. The severity of the pandemic prompted swift action, with the US government alone investing at least $31.9 billion to accelerate the development, production, and purchase of mRNA vaccines against SARS-CoV-2.[8] This substantial investment allowed researchers to formulate, test, and distribute the first doses of both the initial and booster vaccines in record time. However, constantly updating vaccine formulations to combat emerging viral variants is not a sustainable long-term solution. Developing and refining vaccine candidates is a time-consuming and resource-intensive process that can take months or longer, so constantly creating new boosters for each variant would be costly and logistically challenging. Additionally, the rapid pace of viral mutations may outstrip the ability of manufacturers to produce updated vaccines in time, making it difficult to keep up with the evolving virus.

The Ongoing Need for a Broader Solution

A more viable long-term approach would be a universal vaccine capable of offering broad protection against both current SARS-CoV-2 variants and emerging sarbecoviruses, eliminating the need for constant reformulation. This solution addresses the limitations of traditional vaccines by targeting more stable, conserved regions of the RBDs less prone to mutation, which are shared by all existing viruses in the SARS-like betacoronavirus family. The benefits of a universal vaccine are clear: not only would it reduce the frequency of necessary updates, but it would also ensure more consistent protection, better equipping public health systems to manage rapidly evolving viral threats.



CLOSING THE IMMUNITY GAP

The need to develop a broad-spectrum vaccine has sparked an international consortium – including the California Institute of Technology (Caltech), the University of Oxford, engineering biology CRDMO Ingenza, and the UK-based Centre for Process Innovation (CPI) – to initiate development of a novel next generation vaccine against known and future SARS-CoV-2 strains. The principle behind this innovative vaccine project – led by Professor Pamela J. Bjorkman and her team at Caltech, and funded by The Coalition for Epidemic Preparedness Innovations (CEPI) – focuses on directing the immune response toward conserved regions of the RBD shared by viruses in the SARS-like betacoronavirus genus, particularly all sarbecoviruses. This strategy aims to provide broad-spectrum immunity against multiple coronavirus strains, including emerging SARS-CoV-2 variants.

A BIOMANUFACTURING BREAKTHROUGH

The aim of this project is to advance Caltech's 'mosaic-8b' nanoparticle vaccine candidate, which consists of protein-based, self-assembling 60-mer nanoparticles with RBDs from SARS-CoV-2 and seven other coronaviruses arranged randomly on their surface. The key advantage of this design is that it reduces the probability of two adjacent RBDs on the nanoparticle being identical, therefore favoring interactions with B cells with receptors that can preferentially recognize RBD regions conserved across a broad range of coronaviruses. Because these regions should be present and unchanged in all SARS-CoV-2 variants currently in circulation and novel variants that may emerge in the future, as well as other undiscovered sarbecoviruses, mosaic-8 RBD-nanoparticles show promise as a broad-spectrum vaccine candidate.

Initial research published by Caltech and Oxford in 2022 confirmed that these nanostructures effectively elicit protective immune responses against the SARS-like betacoronaviruses that correspond to the components displayed on the nanoparticles, as well as against other related viruses not represented in the mosaic-8b design.[9] This includes coronaviruses found

in animals that could pose a risk of zoonotic transfer in the future. Given that the spillover of animal sarbecoviruses has led to two major outbreaks over the past 20 years – the SARS-1 pandemic in the early 2000s, followed by the COVID-19 pandemic – preventing cross-species transmission is critical for strengthening global pandemic preparedness.

MOVING AWAY FROM CONVENTIONAL HOST PLATFORMS

Ingenza's role in the project was to develop and optimize production of the vaccine components. The biopharmaceutical candidate was initially produced using two common biomanufacturing platforms: mammalian cells for the RBD components and *Escherichia coli* for the nanoparticle scaffold. Mammalian cells are highly effective for producing complex proteins and replicating human biological processes, making them ideal for generating biologically active compounds. However, they also require expensive media – hindering large-scale production of the eight antigen components required for this vaccine candidate – and have a slow turnaround time, which poses a challenge in responding to fast-mutating viruses like SARS-CoV-2. *E. coli* offers faster cell growth and simpler processes, but requires cell lysis and extensive downstream processing to purify the nanoparticle from the host cell proteins and contaminating endotoxins.

To address these limitations, Ingenza transitioned production of the mosaic-8b candidate to the yeast *Pichia pastoris* and the Gram-positive bacteria *Bacillus subtilis*. These microbial platforms offer quicker production cycles, simpler culturing conditions, and the ability to secrete correctly folded recombinant proteins. This makes the production process more efficient and cost effective, leading to a more affordable and accessible vaccine without compromising on quality.

ENHANCING BIOPROCESS DEVELOPMENT

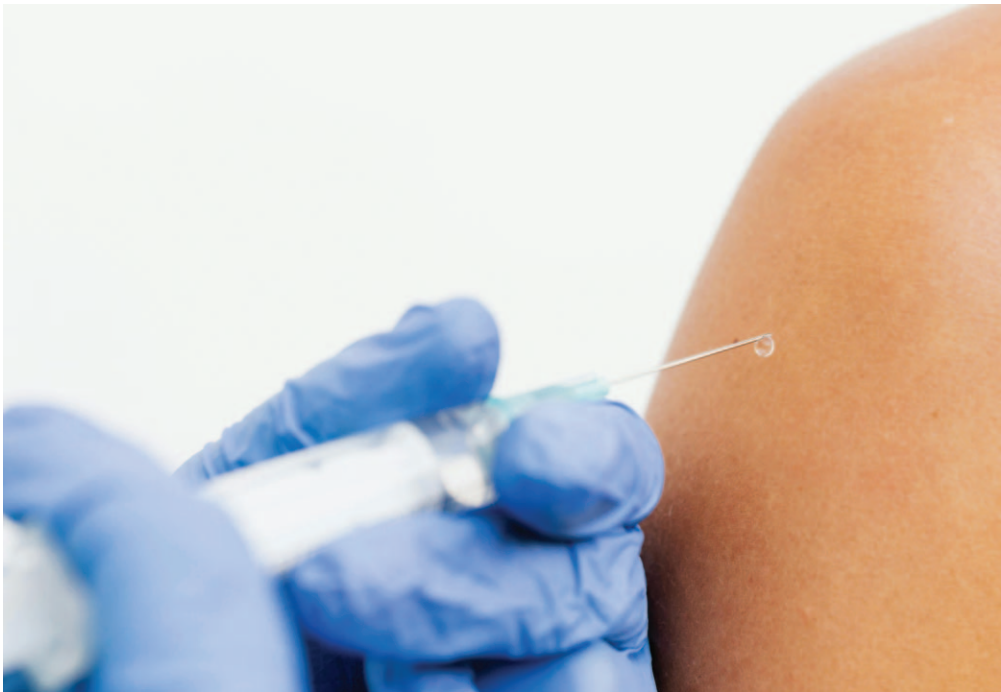
Ingenza harnessed its proprietary *inGenius*™ platform to streamline the vaccine production process, efficiently guiding each step from the creation of custom microbial strains to the development of scalable bioprocesses and generation of material required for preclinical Good Laboratory Practice (GLP) toxicology studies. The platform integrates several modules designed to optimize bioprocess development by selecting the best DNA design and production hosts. Additionally, the *inGenius* platform incorporates essential analytical methods for in-process controls, release assays and drug substance characterization. Centralizing vaccine development within an integrated platform offers a more efficient, predictable, and scalable bioprocess, and decreases the risks typically associated with biopharmaceutical production. It therefore provides a fast, reliable, and cost-effective pathway to market, reducing the costs associated with traditional biomanufacturing processes.

BUILDING ON EXISTING VACCINE IMMUNITY

The widespread transmission of SARS-CoV-2 following the most recent pandemic means that a significant portion of the population has likely encountered the virus by now.[9] This makes it especially important for new vaccines to induce effective immune responses in individuals with previous exposure to the disease or following prior vaccination.

Targeting Various Viral Strains

In the summer of 2022, the mosaic-8b vaccine project secured additional funding and entered extensive preclinical trials to test its ability to generate an immune response in individuals who are not immunologically naïve. The trials demonstrated that mosaic-8b nanoparticles effectively induce production of two types of antibodies: recall antibodies, which boost



the immune system's existing defenses, and cross-reactive *de novo* antibodies capable of targeting a broad range of sarbecoviruses, including those more distantly related to SARS-CoV-2. These antibodies were more effective at recognizing different viral strains compared to those triggered by eight homotypic nanoparticles in the admixture. Additionally, they showed stronger binding and neutralizing abilities than antibodies generated following vaccination with conventional SARS-CoV-2 vaccines, indicating that the mosaic-8b candidate is more versatile in fighting a wider range of viruses.

Overcoming Original Antigenic Sin

The preclinical trials also offered valuable insights into the phenomenon of original antigenic sin (OAS), where the immune system tends to rely on memory cells formed during an initial exposure to the virus when encountering related antigens.[10] This can limit the immune system's ability to respond effectively to new variants. The mosaic-8b vaccine showed promise in overcoming this issue, by generating new antibodies that target a range of sarbecovirus RBDs, rather than merely enhancing the production of existing antibodies specific to certain SARS-CoV-2 strains. These findings suggest that a single dose of this vaccine could stimulate a stronger and broader immune response in individuals who are not immunologically naïve compared to a single dose of a standard SARS-CoV-2 homotypic vaccine. This would mean longer-lasting protection against a wider range of SARS-CoV-2 strains and other sarbecoviruses.

SUMMARY

Although the mosaic-8b vaccine is still in early development, it has the potential to enable a broad and cross-reactive immunization strategy that could provide comprehensive protection against known and unknown sarbecoviruses. The mosaic-8b nanostructure could also serve as a template for developing next generation vaccines that do not need frequent updates or iterations, unlike monovalent or bivalent vaccines targeting specific variants. The next phase of this groundbreaking project is to advance the mosaic-8b vaccine candidate into the final round of preclinical trials, with the goal of entering human clinical trials in the near future, moving closer to a market-ready vaccine. With a multi-pronged defense system that is resilient to viral escape, this next generation vaccination strategy can enhance our protection against various viral strains, both now and in the future. ◆

REFERENCES

1. World Health Organization. (2024). WHO covid dashboard. https://data.who.int/dashboards/covid19/deaths.
2. Watson, O.J. et al. (2022). Global impact of the first year of COVID-19 vaccination: A mathematical modelling study. The Lancet Infectious Diseases, 22(9), 1293-1302. doi: 10.1016/s1473-3099(22)00320-6.
3. World Health Organization. (2024). COVID-19 vaccinations have saved more than 1.4 million lives in the WHO European Region, a new study finds. https://www.who.int/europe/news/item/16-01-2024-covid-19-vaccinations-have-saved-more-than-1.4-million-lives-in-the-who-european-region-a-new-study-finds.
4. Sanjuán, R., & Domingo-Calap, P. (2016). Mechanisms of viral mutation. Cellular and molecular life sciences: CMLS, 73(23), 4433-4448. doi: 10.1007/s00018-016-2299-6.
5. Willett, B.J., Grove, J., MacLean, O.A. et al. (2022). SARS-CoV-2 Omicron is an immune escape variant with an altered cell entry pathway. Nature Microbiology, 7, 1161-1179. doi: 10.1038/s41564-022-01143-7.
6. Bergwerk, M., Gonen, T., Lustig, Y., et al. (2021). COVID-19 Breakthrough Infections in Vaccinated Health Care Workers. The New England journal of medicine, 385(16), 1474-1484. doi: 10.1056/NEJMoa2109072.
7. Beukenhorst, A. L., Koch, C. M., Hadjichrysanthou, C., et al. (2023). SARS-CoV-2 elicits non-sterilizing immunity and evades vaccine-induced immunity: implications for future vaccination strategies. European journal of epidemiology, 38(3), 237-242. doi: 10.1007/s10654-023-00965-x.
8. Lalani, H.S., Nagar, S., Sarpatwari, A., et al. (2023). US public investment in development of mRNA COVID-19 vaccines: retrospective cohort study. BMJ (preprint). doi: 10.1136/bmj-2022-073747.
9. Cohen, A. A., van Doremalen, N., Greaney, A. J., et al. (2022). Mosaic RBD nanoparticles protect against challenge by diverse sarbecoviruses in animal models. Science, 377(6606), eabq0839.
10. Cohen, A. A., Keeffe, J. R., Schiepers, A., et al. (2024). Mosaic sarbecovirus nanoparticles elicit cross-reactive responses in pre-vaccinated animals. Cell (published online ahead of print), 187, 1-18. doi: 10.1016/j.cell.2024.07.052.

BIOGRAPHY

Dr. Leonardo Magneschi is Vice President of Research and Technology Development at Ingenza. He has more than 15 years of experience in microbiology and genetic engineering, with a PhD in Plant and Microbial Biotechnology, 17 published papers in peer-reviewed scientific journals, and inventorship on several international patents. He joined Ingenza in 2016 and has since been directly involved in a multitude of customer projects, with applications ranging from pharma and biofuels to renewable materials. He can be reached at Leonardo.magneschi@ingenza.com.

Special Feature

Analytical Testing – Diverse Demands & Therapies Require Diverse Analyses

By: Cindy H. Dubin, Contributor

The global market for pharmaceuticalanalytical testing outsourcing was estimated at $10.3 billion in 2023 and is projected to reach $16.3 billion by 2030.[1] Rising complexity of drug molecules, particularly in the biologics and biosimilars sector, and a growing demand for personalized and specialized medicines, require more sophisticated analytical testing methods to ensure safety, purity, and efficacy, which often necessitate the use of highly specialized equipment and expertise. Additionally, rapid advancements in digital technologies and data analytics have made outsourcing an attractive option for pharmaceutical companies. Contract Research Organizations that offer advanced data analytics capabilities can provide deeper insights into testing results, accelerating decision-making and improving the overall efficiency of drug development.

As is occurring in many industries, Artificial Intelligence (AI) is disrupting pharmaceutical analytical testing. The combination of AI and automation will drive substantial progress, making pharmaceutical analytical testing more cost-effective. As a tool for predictive analytics in pharmaceutical development, AI accelerates market entry of new pharmaceuticals and improves accuracy in intricate testing situations.[2]

This exclusive, annual *Drug Development & Delivery* report highlights how analytical testing has evolved to address diverse pharmaceutical therapeutics in research and development.

One of three global locations, Aliri Bioanalysis's laboratory in Lille, France, specializes in using spatial bioanalysis to quantify drug exposure and biomarkers of efficacy at the site of action.

Aliri Bioanalysis: Validation Studies Save Time & Money

The biopharma industry has seen a significant increase in demand for the analysis of oligonucleotide therapeutics given their potential to change the standard of care for a wide range of diseases. This has led to the critical application and optimization of available analytical approaches, including LC/MS/MS, hybridization LC/FD, LC/HRMS, and hybridization ELISA assays. Aliri has more than 30 years of expertise weighing the advantages and limitations of these methods, and looks for ways to innovate and improve assay sensitivity and specificity to deliver accurate and reliable data for its sponsors, says Troy Voelker, PhD, Senior Director of Laboratory Operations at Aliri Bioanalysis.

Aliri is known for taking on some of the most challenging projects and rescuing studies when other labs may fail. "We are quite used to developing and validating custom assays for sponsors, usually in a matter of days, to keep their development projects on track," says Shane Karnik, Senior Laboratory Director at Aliri Bioscience. "Our team acts as a collaborative partner using our experience to provide expert guidance and suggest analytical methods that yield better data."

Aliri's customers are prioritizing fast timelines and off-the-shelf, affordable solutions, as opposed to highly customized analytical methods, which can be quite costly and take time to develop. As a result, Aliri offers hundreds of non-proprietary, validated assays and biomarker panels that keep costs low and get meaningful data in customers' hands quickly.

Jim Wilfahrt, Chief Operations Officer at Aliri Bioscience, says the company tackles complex studies across all modalities and seeks to find innovative solutions to meet challenging molecules and timelines. "We've also rescued many programs that hit a wall at other labs," he says. "One customer told us that when three other labs failed, Aliri was their last hope. We not only found a solution that worked so their program could proceed, but in the process, saved that biotech company from certain collapse."

Time savings is the reason Aliri Bioanalysis has integrated Artificial Intelligence (AI) with spatial-omics data, resulting in earlier prediction of the efficacy of targeted therapies – thereby enhancing customers' candidate selection processes and de-risking development programs. At a recent conference, Aliri presented an in-depth analysis of complex biological datasets demonstrating how spatial-omics capabilities are an enabler for predictive science.

"Aliri's data scientists are leveraging custom AI scripts to help our sponsors identify and better understand the drug mechanism of action at the single-cell level with far greater certainty than traditional methods," says Corinne Ramos, PhD, R&D Director, Aliri Bioanalysis. "The power of AI in conjunction with genomic, proteomic, and metabolomic analysis is a game-changer that provides our clients an edge when selecting drug candidates that are most likely to succeed in the clinic – while saving them time, money, and from costly mistakes in the process."

Almac Sciences: Analytics to Advance Human Health

Almac continues to significantly enhance its analytical services through several key initiatives positioning the company as a versatile and reliable partner, capable of meeting evolving client needs. Investing almost $14 million to expand analytical services globally, lab footprint and capabilities have considerably increased throughout their facilities in Europe and the US. Inside the lab, investments include specialized equipment, such as a Raman TRS100 system for faster analysis, a multi-million-dollar upgrade to the Laboratory Information Management System (LIMS) to enhance information sharing and optimize operations, as well as other physical sciences tools to support new offerings, like spray drying for poorly soluble drugs.

"This all enables Almac to offer a full suite of analytical testing for various product types, ensuring the ability to handle diverse challenges across all phases of drug development," says Darren Thomas, Vice President Analytical Operations, Almac Sciences.

Almac has also focused on industry collaborations to advance its analytical testing capabilities. "These partnerships have enhanced our services, integrated innovative technologies, and adapted to evolving industry needs, leading to more efficient and sustainable research and quality control processes," he says. "Our collaborative approach has proven to be instrumental in achieving remarkable outcomes in analytical testing. We remain dedicated to fostering these partnerships, driving innovation, and delivering exceptional value to our clients and the wider industry."

In addition to fostering collaboration, Almac is exploring several initiatives where Artificial Intelligence could deliver benefit to its testing services. Some examples are standard operating process creation/update; instrument and people scheduling; instrument utilization; quote generation; regulatory changes and impact; human error trending; and report review/data checking.

"Our investment in robotics revolutionized the dissolution space by providing unmatched throughput capabilities and 24/7 operation," says Mr. Thomas. "The robot's compact footprint and superior quality control, including visual assessments and high repeatability, ensure minimal variance and high results. This leads to increased productivity and enhanced service quality for our clients."

Providing quality services to clients is exemplified in a drug substance and drug product stability program. He explains that the stability study involved thorough analytical testing and preparation methods to ensure the stability of both API and the drug product. Key efforts included the validation of analytical methods, preparation of samples, and the establishment of stability conditions over five years. The study also incorporated transport and in-use stability trials to simulate real-world conditions.

"The project emphasized efficiency by consolidating processes and minimizing setup times, saving significant lab time," Mr. Thomas says. "The client was satisfied with the comprehensive data, which informed decisions for their Phase III study."

Inotiv: Expanding Services to Address Diverse Therapies

The emergence of novel biotherapeutics has had a major impact on bioanalytical laboratories and it requires laboratories to offer a wider range of services with more sensitive bioanalytical techniques, which sometimes produce larger sets of data to be analyzed and interpreted.

"Traditionally, most of the drugs were small molecules requiring LC-MS bioanalysis, and for some of the large molecules, basic ELISA and RIA support were sufficient," explains Kenneth Swart, MMedSc, PhD, Senior Vice President Biotherapeutic Sciences, Inotiv. "With the introduction of large molecule protein drugs such as antibodies, fusion proteins, growth factors and recombinant peptides, traditionally used LC–MS methods were inappropriate to analyze these molecules, although today, much progress has been made in this field. The greater size and complexity of these molecules normally require extensive sample preparation as well."

Originally, the dominant form of bioconjugates were antibody drug conjugates (ADCs) and used in oncology. Recently, the implementation of bioconjugate therapeutics has been expanded into immunosuppressive, anti-inflammatory, and antimicrobial indications. For an ADC treatment, an antibody targets a specific receptor expressed by cells, and an attached drug (payload) mediates the therapeutic response. Analysis of both the biomolecule and the payload using different techniques are required, explains Dr. Swart.

The analysis of cell and gene therapeutic agents, including oligonucleotides, requires additional bioanalytical technologies such as ELISpot, different forms of hybridization immunoassays (HELISA), qPCR, and flow cytometry platforms. It also requires the analysis of the AAV capsid, and transgene expressed proteins in different tissue samples.

A challenge in drug development is how to measure the ability of a target system to respond to a drug treatment because it would require direct quantitative analysis of cells and tissues including FFPE treated cells. The ability of a target system to respond to a drug depends on:

- The abundance of the target;
- The abundance of other key system proteins; and
- Other proteins that control the tissue phenotype.

Dr. Swart says: "These are very difficult to measure quantitatively due to the complexity and condition of different ma-

Inotiv scientists performing analytical testing on biotherapeutics.

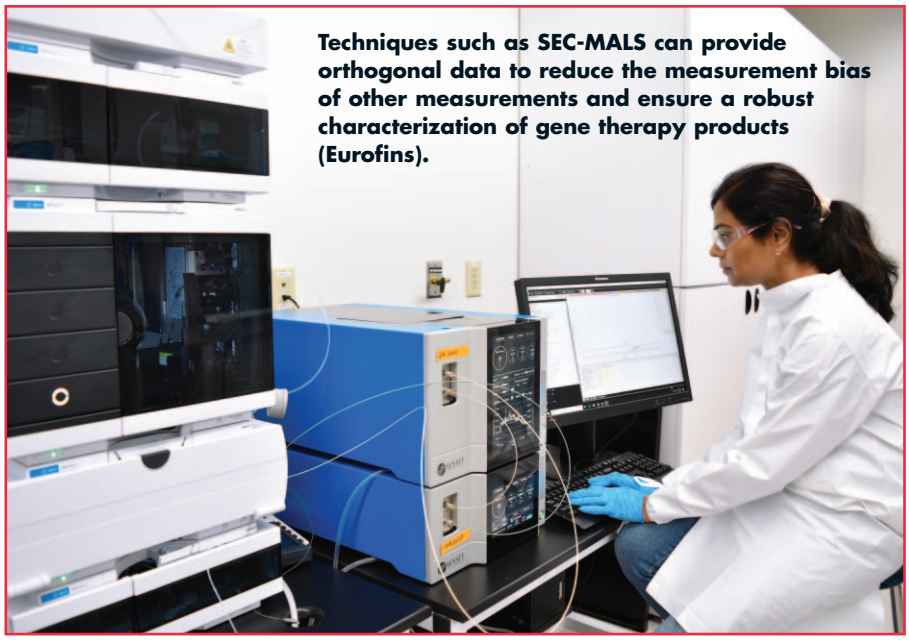
trices and tissue samples. Since immunohistochemistry is not quantitative enough, alternative techniques are required such as high resolution mass spectrometry. This has required bioanalytical scientists to attain a much higher level of expertise in the field of immunochemistry, mass spectrometry, immunology, and molecular biology."

Therefore, depending on the structure of the molecule, stability of the compound, matrix interferences, and other complexities, techniques such as LC-MS, LC-high resolution MS, hybrid LC/MS, flow cytometry, and more sensitive ligand binding assays, are required. Drug development also requires the implementation of comprehensive bioanalytical solutions spanning from discovery to full GLP/GCLP analysis of small molecules, monoclonal antibodies, and novel biotherapeutics. This includes method development to full validation for PK, immunogenicity, receptor occupancy, biodistribution in different tissues, and a full biomarker analysis solution. "Inotiv has expanded and refined our services to meet these diverse and evolving demands of drug development," he says.

Eurofins Biopharma Product Testing: Developing Pipelines for Cell, Gene & mRNA Therapies

Cell, gene, and mRNA therapies have gained significant momentum. In response, laboratories must expand their testing portfolio to include bioassays, which may require expertise in cell culture, ELISA, PCR, and flow cytometry.

While long-standing technologies such as HPLC and mass spectrometry are utilized in a gene therapy workflow, the variety of genome delivery systems requires an increasingly diverse and complex array of instrumentation and expertise to fit into that workflow. Incorporating new technologies that achieve identical results with reduced sample volume and concentration is a critical initiative to broaden the scope of cell and gene solutions.



Techniques such as SEC-MALS can provide orthogonal data to reduce the measurement bias of other measurements and ensure a robust characterization of gene therapy products (Eurofins).

"One analytical technique that has delivered on this is mass photometry, which allows for quantitation of empty, full, and partially filled AAV capsids and produces similar results to analytical ultracentrifugation (AUC)," says Jeremy Johnston, Scientific Advisor, Drug Product Operations, Eurofins BioPharma Product Testing. "The advantages of this assay are speed (2 minute vs. 24+ hour analysis time) and sample volume (10μL vs. 0.5 – 1mL) needed for analysis."

He adds that in potency development, Eurofins BioPharma Product Testing utilizes a stepwise approach to viral vector potency assay development to effectively demonstrate *in vivo* activity. "We work with clients in the early phases to develop assays to show expression of protein transgene product by capillary western blot or ELISA," he explains.

For Mechanism of Action (MOA) determination, other instrumentation such as Flow Cytometry or Meso Scale Detection are often implemented. Over the course of product development, the potency testing strategy can be refined, leading to partition between methods intended for lot release vs. characterization based on both scientific and practical considerations.

"We align with others in the cell and gene therapy field to ensure we are well positioned to create partnerships that enable change and accelerate development of life-saving modalities to the market quickly, while ensuring accurate quality standards," says Mr. Johnston.

As an example, during the COVID-19 pandemic, Eurofins BioPharma Product Testing tested several COVID-19 therapies that clients developed and received regulatory approval. "In addition to our 24/7 rapid-response sample management and testing services, vast capabilities, and quality systems, these projects used our secure online real-time data access portal LabAccess® Web Services to directly integrate data into our clients' LIMS to ensure expedited and seamless product release to the market," he says. "By having redundant technology for LNP analysis and

characterization, we were able to meet timelines and ensure quality while working across multiple departments to bring life-saving vaccines and treatments to patients."

Lifecore Biomedical: Expertise in Complex & Highly Viscous Formulations

Lifecore Biomedical continually expands its analytical offerings to meet customer demand for faster testing turnaround with a more diverse range of analyses. In recent years, the company built a new laboratory to accommodate sub-visible particulates testing. The new laboratory was designed with heightened environmental controls to ensure accurate results for parenteral products, especially in the area of ophthalmics, which has extremely strict particulate requirements. "We implemented instrumentation for both light obscuration and microscopic methodologies to support customers with different sample types and testing needs," says Kevin Vickerman, PhD, Senior Scientist at Lifecore Biomedical.

With expertise in complex and highly viscous formulations, test methods for new products require creative problem-solving. Dr. Vickerman explains a recent customer approached Lifecore Biomedical to improve their viscosity testing of a viscous drug product. The customer was not seeing any correlation between release and stability results, or results between manufacturing lots.

"To troubleshoot the variability of this method, we performed a shear-sweep experiment demonstrating the material was shear-thinning with no Newtonian regions suitable for simple apparent viscosity testing," he says. "Given this, we proceeded to characterize the viscoelastic properties of the material using an oscillatory method on a rheometer, allowing us to measure the phase shift between stress and strain, and the complex modulus of the material. From there we evaluated the yield stress with steady stress sweeps and dynamic stress/strain sweeps. Ultimately, we developed a dynamic stress sweep method to determine the yield stress (onset point) of the material. We then established a specification for yield stress of the material and successfully validated the test method to support the customer's registration campaign."

Lifecore Biomedical brought particulate testing in-house to provide rapid turnaround of customer results.

Overall, Dr. Vickerman says the improved method is easier to execute, highly repeatable (allowing for meaningful batch comparison and trending), and ultimately allowed the customer to quantify subtle material differences across the fill of a production lot that were not apparent from assessment of other CQAs (i.e. assay).

MilliporeSigma: Meeting the Diverse Needs of Viral Vectors

Critical for the robust development and production for viral vectors, analytical testing is an essential component of the majority of cell and gene therapies in development today. Each of these complex therapeutics rely on a distinct and comprehensive analytical program to measure critical quality attributes (CQAs), as well as drive process optimization, yields, and product quality. A challenge with viral vectors, as compared to recombinant proteins and other complex biologics, is the inherent high degree of complexity needed for characterization and QC testing due to their varying protein assembly and architecture. This requires the development and validation of specific analytical methods for different vector types, as well as product-specific assays for potency and product-related impurities, in addition to process-related impurities.

To meet the diverse viral vector characterization and process and product testing needs, MilliporeSigma recently completed an expansion of its analytical development and QC labs at its Carlsbad, CA facility. "In addition to increasing our on-site footprint, we added advanced instrumentation to provide more well-rounded support for a range of viral vectors and incorporated new technologies to allow us to develop methods to

MilliporeSigma uses automated and high-throughput solutions to streamline analytical workflows resulting in faster, more consistent processes to gain actionable insights at its viral vector CDMO.

support the characterization and testing of our clients' cell and gene therapy programs," explains Michael Shen, PhD, Head of Process & Analytical Development, Viral Vector CDMO, MilliporeSigma. "Augmenting traditional analytical instruments with next-generation technologies such as short and long read next-generation sequencers allow us to characterize AAV therapies at multiple points during the development and manufacturing process, allowing our scientists to identify a gene of interest (GOI), verify its length, and pinpoint any mutations that might have occurred, which may impact potency or produce off-target effects." Other highly specialized instruments, like mass spectrometers, can help identify post-translational modifications that may affect long-term stability or its infectivity, which may be detrimental to product stability and potency.

Additionally, incorporating a data-driven approach during the development process helps prioritize those critical analytics that help drive product and process-related insights and inform real-time decision making, especially as the program scales, he says. Automated analytical methods, which enable high-throughput testing, help deliver this data, thereby accelerating development timelines. He says: "We use high-throughput sampling and automated instruments to achieve more thorough characterization, as well as automated workflows to extract DNA, and plate or prep various dilutions with our robotic workstations for nano-digital PCR tests for host cell DNA."

He adds that MilliporeSigma's analytical development team works closely with the process development team to provide high-throughput analytical support process design. "We recently had a client looking to optimize their process to achieve more product during production," Dr. Shen says. "Concurrent to the process optimization studies, custom assays to confirm titer and potency needed to be developed. The analytical development team supported the testing needed by the process development team during the execution of small-scale screening studies to determine optimal results. They were able to customize an off-the-shelf assay to meet the testing needs of the client's product. This allowed the client to accelerate their development timeline by 2.5 months and initiate the manufacturing program for their clinical trial."

Stevanato Group: Optimizing Product Design & Manufacturing

Cell and gene therapies and mRNA drug products are often particularly sensitive to product loss – with some therapies costing millions of dollars, mitigations against losing product are paramount. For example, the risk of losing contents from a dropped container must be minimized. Mechanical testing – such as drop or burst tests – on a variety of container options after the thermal stress of storage can identify the most robust solution. Helium leak and laser headspace gas analysis can also check container closure integrity at extremely low storage temperatures. If the API adheres to the inner surface of a container, the total deliverable volume or drug concentration may be lower than acceptable. For proteinaceous drug compounds, this can be worsened by inner surface variations. Differential interference contrast microscopy, scanning electron microscopy, and optical profilometry can help compare different container providers both initially and over the product's anticipated shelf life.

Stevanato Group's initial offering in 2014 studied how drug interacted with a glass container, i.e. glass delamination. Since then, its services have expanded to cover a range of mechanical, systemic, and chemical testing, including syringe, cartridge, and delivery device performance testing, as well as material identification and quantification – all of which can be used to better understand and optimize product design and manufacturing processes. With the opening of a US Technology Excellence Center (TEC) in Boston in 2020, the company began studying the

Helium leak analysis to check container closure integrity at Stevanato Group.

impact of fill and finish activities, which can improve downstream product testing and the qualification of high-speed inspection and assembly equipment.

"Today, we are implementing new capabilities to characterize drug quality over time – to see how the drug itself degrades in the presence of the container," says Alan Xu, Product Manager for Analytical Services, Stevanato Group. "Techniques like fluorescence, light scattering, and UV-Vis spectroscopy will help us study proteins, viral vectors, and nanoparticles in addition to the overall container and device performance."

Both the US TEC and EMEA TEC focus on centralized testing and minimize the number of destroyed samples as Xu says Stevanato Group's offerings can be designed to use the same samples for multiple tests that do not interfere with each other's performance. Finding the right product – or eliminating the wrong ones – earlier is also speeding up the decision-making process and reducing wasted commercialization effort.

Stevanato Group has a partnership with Roche, resulting in Stevanato Group's Vision Robot Unit (VRU) inspection technology being installed on Roche's manufacturing line to complement its own checking equipment. The higher performance of the VRU means fewer samples need to be tested – and results are available within minutes instead of days, states Xu.

Time was also critical for a client that came to Stevanato Group with a mAb in development for the treatment of an immunological disorder. It was crucial to find a containment and delivery system that would ensure the quality, safety, efficacy, and stability of the drug.

"At the earliest stages, we combined analytical testing – such as delamination and protein adsorption studies – to screen multiple container candidates to find the right solution as soon as possible," he says. "Our collaboration has saved them up to two years of development time, including time that would have been lost since they had originally selected a suboptimal container." ◆

References

1. Pharmaceutical Analytical Testing Outsourcing Global Business Analysis Report 2024-2030: Emerging Use for Preclinical and Clinical Trials Fuels Growth in Early-Stage Drug Development, ResearchandMarkets, Dec. 4, 2024, https://www.businesswire.com/news/home/20241204243334/en/Pharmaceutical-Analytical-Testing-Outsourcing-Global-Business-Analysis-Report-2024-2030-Emerging-Use-for-Preclinical-and-Clinical-Trials-Fuels-Growth-in-Early-Stage-Drug-Development---ResearchAndMarkets.com.
2. AI and automation to drive "substantial progress" in pharmaceutical analytical testing, Nov. 25, 2024, https://www.europeanpharmaceuticalreview.com/news/238259/ai-and-automation-to-drive-substantial-progress-in-pharmaceutical-analytical-testing/.

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OUTSOURCING PHARMA DEVELOPMENT

Harnessing CDMOs for Innovation & Efficiency

By: Rohtash Kumar, PhD

INTRODUCTION

The global pharmaceutical industry is evolving rapidly with continuous new therapeutic modalities and manufacturing technologies in development. Progress has transformed patient outcomes by facilitating access to much needed treatment options across diverse therapeutic areas. This progress brings opportunities and challenges for developers.

Most notably, increased demand for innovative pharmaceuticals has required focus on maximizing drug development efficiency and cost-effectiveness. Developers must also navigate the ever-evolving regulatory landscape and ensure consistent manufacturing of safe, efficacious products at the scale required to meet global patient needs.

Contract development and manufacturing organizations (CDMOs) have become an integral part of the pharmaceutical industry by supporting developers to manage the growing intricacies of process development throughout the drug lifecycle.[1] CDMOs offer specialized services and technologies to solve the challenges of complex development and manufacturing projects from early drug development stages through to scale up. They excel in facilitating efficient and cost-effective project delivery, supplying integrated end-to-end capabilities and providing dedicated expertise, which all reduce time to market and ensure continuous high quality.

INCREASING ACTIVE PHARMACEUTICAL INGREDIENT (API) COMPLEXITY

The demand for novel pharmaceuticals has grown across the industry to reach more medical indications with high specificity and efficacy. While this delivers significant benefits for patients, it presents a new challenge for developers – increased API complexity.

For example, more complex API molecules with higher molecular weights and more chiral centers are increasingly popular drug candidates due to their improved stereoselectivity, enhanced target specificity, and increased drug activity. However, these same molecular characteristics can tend toward poor solubility and bioavailability. Challenges are further compounded by the continued preference for solid dose forms which require developers to overcome inherently low absorption of these complex APIs within the gastrointestinal tract.[2]

Alongside chemically complex APIs, highly potent APIs (HPAPIs) are also growing, especially in the development of antibody-drug conjugates (ADCs). ADCs consist of a monoclonal antibody attached to a cytotoxic HPAPI via a chemical linker. The antibody delivery mechanism targets specific cancer cells for drug release, which helps to increase efficacy and reduce the side effects of conventional chemotherapy. This therapeutic advancement involves careful management of HPAPIs, as they present additional safety and regulatory challenges compared to traditional APIs due to their high toxicity.[3]

These trends have led to a significant paradigm shift in the development process. To mitigate the challenges associated with more complex and potent APIs, developers are looking to utilize advanced delivery systems and state-of-the-art engineering techniques. Niche, complex drug substances and forms require specialized knowledge, equipment, and technologies that would require large investments for many developers to add to their core drug discovery and product management foci.

OVERCOMING API CHALLENGES WITH A CDMO

Many challenges can arise when developing and formulating therapeutics with complex APIs. CDMOs' specific capabilities and expertise help developers successfully overcome formulation difficulties and may be demonstrated by exploring three challenge areas and their solutions through CDMO expertise and capabilities: (1) improved physiochemical properties through solid form selection, (2) increased stability, solubility, and bioavailability through particle engineering, and (3) safe and effective handling of potent compounds through established expertise and infrastructure.

Solid Form Selection

One of the primary challenges during the early stages of API development is identifying the optimal crystalline structure of the drug compound. Different crystalline/polymorphic forms often exhibit different physiochemical properties. Solid form selection represents a key opportunity to optimize drug performance.

The importance of crystalline form is underscored by the regulatory requirement for polymorph assessment to validate the final drug product stability, efficacy, and safety for patients. Notably, solid form selection and control reduces off-target activity caused by interactions of different polymorphic forms of the drug compound within the body. The polymorphic form also influences the yield and purity of the active drug substance as well as formulation options for the final drug product. The latter is especially vital to optimize pharmacokinetic properties such as absorption.[4]

CDMOs can provide a wide range of services to help accelerate solid form selection, ensure consistent manufacture of the optimal form, and maintain regulatory compliance. This includes offering specialized skills and state-of-the-art equipment to leverage advanced screening techniques such as single-crystal x-ray diffraction (SCXRD). Specific chiral screening services can also be provided to support developers working with chiral APIs and intermediates.

Many CDMOs also offer additional testing capabilities to help developers identify further opportunities for enhancing physical properties of their compound. Using techniques such as salt and co-crystal screening, CDMOs can provide tailored recommendations to help improve solubility, bioavailability, stability, and purity, which supports the development of an optimized drug product.

Particle Engineering

Optimizing the physical properties of complex drug compounds may also challenge API development. By enabling the formulation of compounds into forms with more favorable shapes, sizes, and surface areas, particle engineering can enhance solubility, stability, and bioavailability.

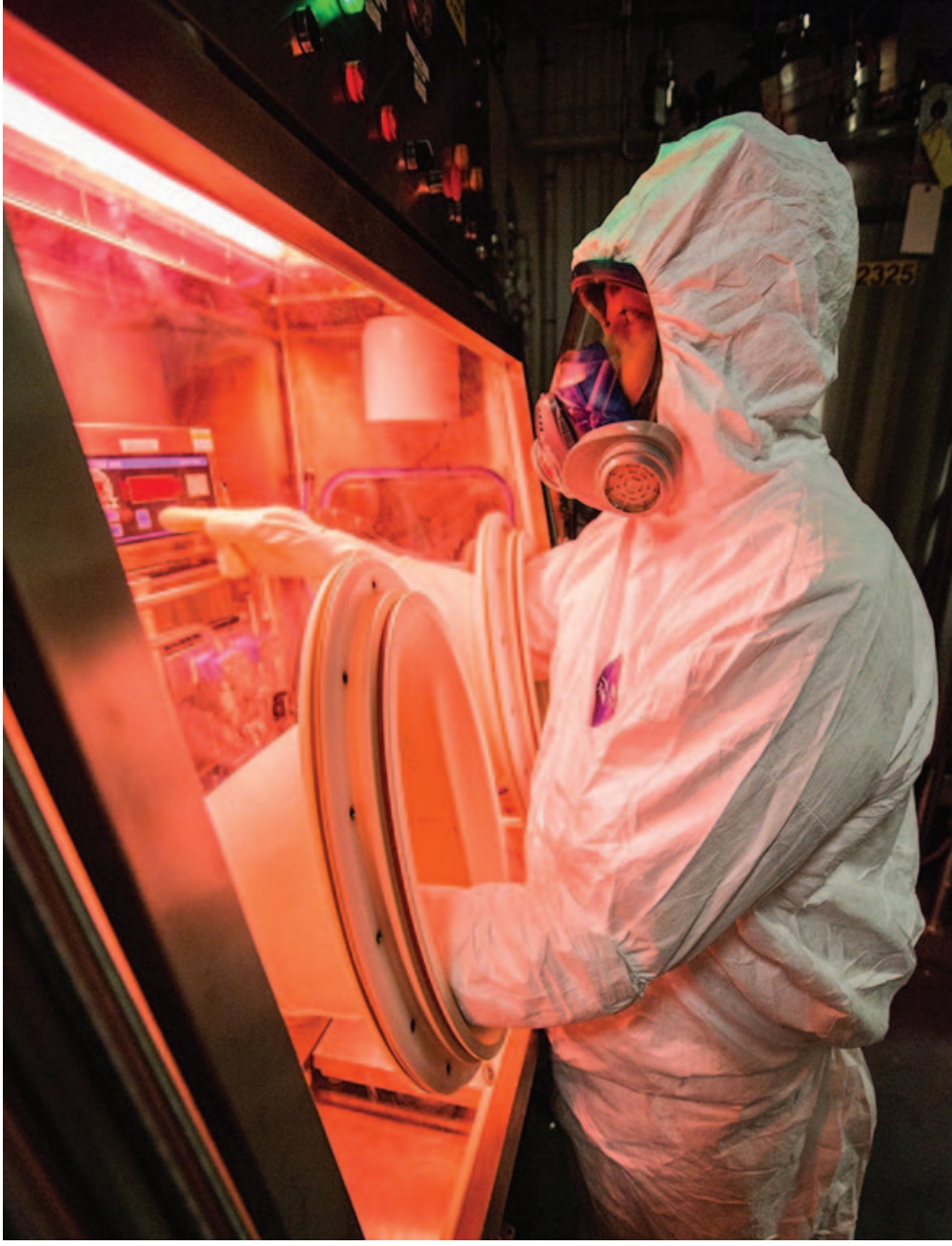
It is key to optimize the physical properties of complex compounds as early as possible in the development process. Progressing compounds with poor solubility, instability, or low bioavailability can result in considerable additional work to overcome these deficiencies. If physical properties are optimized later in the development process, the costs can increase and ultimately delay commercialization.[5] Taking a proactive approach has become a priority for developers. However, the knowledge and technical capabilities required can present a high barrier to entry.

For instance, creating an amorphous solid dispersion (ASD) using a polymer

matrix is a popular approach to increase solubility and bioavailability. ASD requires consideration of many interacting variables, which requires extensive experience and knowledge for its successful use. Developers need to ensure that the overall physical stability of the drug is not negatively impacted. This involves having the expertise to identify, screen, and validate a suitable polymer that delivers the required drug properties and scales to an optimized large-scale production process.[6] Likewise, for developers looking to reduce the physical particle size of their APIs, identifying the optimal particle size can be difficult without previous experience within this area.

In addition to characteristic selection, ascertaining the best manufacturing approach to achieve the desired physical and functional properties of the drug compound can present difficulties. Spray drying and hot melt extrusion have emerged as effective options for ASD development.[7] Similarly, for developers looking to achieve sub-micron particle sizes, promising options include state-of-the-art approaches like nano-milling and high-pressure homogenization.[8] Each of these techniques require specialized equipment. Therefore, without considerable investment, developers can struggle to independently implement these technologies in their development and manufacturing workflows.

Working with a CDMO with particle engineering experience can help developers find the optimal solution for their API's physical properties. As a long-term manufacturing partner, a CDMO can enable developers to reap the benefits of advanced particle engineering techniques without the need for costly additional equipment or time-consuming in-house training.



Handling Potent Ingredients

For developers working in the field of personalized medicine, ADCs offer considerable opportunities to innovate new, targeted therapies for a range of different types of cancer, but working with ADCs and their HPAPI constituents requires the utmost care and specific experience with relevant regulations, analytical techniques, separations, and complex chemistry.

HPAPIs need to be carefully managed throughout the entire process lifecycle of ADC manufacturing to ensure safety for manufacturing staff and patients.[9] This includes building specialized containment infrastructure that often requires significant investment. Additionally, regulatory bodies are increasingly focused on ADC manufacturing process optimization to ensure consistent quality.[10] As a result, working with a CDMO that is equipped to safely handle HPAPIs and manufacture consistent ADCs can help developers to reduce overall costs and ensure regulatory compliance.

ADCs are multi-component therapeutics, and their development can present unique complications. A complex part of an ADC's design is the linker molecule, which must maintain stability during preparation, storage, and systemic circulation. Then, it must release the HPAPI at

the specific target site within the body. In addition, accurately characterizing these therapeutics is difficult, because it requires combining several analytical, biochemical, and biophysical techniques.[11] Within this area, chromatography expertise and capacity are especially valuable to support developers in accurate compound characterization and effective ADC purification.

CHOOSING A CDMO TO SUPPORT SUCCESS

A strategic partnership with a trusted CDMO can provide many benefits ranging from experts' insights to state-of-the-art equipment. However, there are several considerations that developers should evaluate prior to engaging with a CDMO to maximize their partnership.

Developers must carefully assess the need for a CDMO partner before commencing their project. Early involvement of a CDMO ensures valuable partnered input into the planned development approach. Leveraging a CDMO's expertise at an early stage can significantly reduce the risk of unforeseen challenges and associated costly delays arising down the line.

Developers need to choose a CDMO that is capable and adept at the unique requirements of their project. The CDMO should have specific expertise and proprietary technology to support particularly complex areas of development such as solid form selection, particle engineering, and highly potent API handling. To maximize confidence, developers should search for CDMOs with capabilities in these areas and a proven track record of successful project delivery and quality.

In addition to the CDMO's development capabilities, developers should evaluate its technology transfer approach to ensure streamlined project delivery. Knowledge and technologies need to be shared at multiple phases of the development process and throughout the product lifecycle. Due to the complexity of pharmaceutical manufacturing, close collaboration between process engineering and development, analytical chemistry, quality, and production teams is essential at every stage. Choosing a CDMO with a well-defined technology transfer approach that is managed by an experienced, multi-disciplinary team is essential to ensure efficient scale-up and support long-term success.

The capacity and regional capabilities of the prospective CDMO should also be considered. Working with a CDMO that has a network of sites offering specific capabilities with established technology transfer processes between them, ensures developers can access specialized support in line with their needs. Moreover, with multiple sites, developers can be confident that the CDMO has the bandwidth to provide dedicated and responsive service at every stage of the development and manufacturing process.

While evaluating a CDMO's experience and capabilities should be a priority, the importance of aligned working practices should not be overlooked. For example, developers should ensure that the CDMO can provide an integrated project management approach. This approach facilitates the CDMO to work seamlessly with the developer's internal team. Evidence of the CDMO's commitment to collaboration, transparency, and clear communication can reassure developers that they are working towards a shared goal with a dependable partner.

MANAGING COMPLEXITY WITH CONFIDENCE: THE NEED FOR OUTSOURCING

As innovation continues across the pharmaceutical industry, developers must keep pace with new technologies, emerging research, and evolving regulations. However, with many companies managing short timelines, tight budgets, and limited internal bandwidth, this can be difficult.

CDMOs offer specialized expertise and advanced technical capabilities to support developers on the growing complexities of drug development. Developers that partner with a CDMO successfully and cost-effectively navigate the challenges of innovative pharmaceuticals development. Moreover, with CDMOs increasingly offering agile and specialized services, developers can receive targeted, expert support to help overcome specific development challenges, from particle engineering to HPAPI handling.

Ultimately, by partnering with a trusted CDMO, developers can confidently embrace innovation, overcome development challenges, and accelerate commercialization to drive the delivery of life-saving treatments to the patients who need them. ◆

REFERENCES

1. CPHI Online. Global CDMO Trends: the 2024 outsourcing forecast. https://www.cphi.com/content/dam/esa/hn/cphi/en/brochures/CPHI-trend-report-outsourcing-trends-and-strategies.pdf. Published April 2024. Accessed June 27, 2024
2. Thomas F. Adapting to Solubility/Bioavailability Challenges. Pharmaceutical Technology 2022; 46(8). https://www.pharmtech.com/view/adapting-to-solubility-bioavailability-challenges
3. Hotha K. Antibody-Drug Conjugates (ADCs): Navigating Four Pillars of Safety, Development, Supply Chain and Manufacturing Excellence. Advances in Chemical Engineering and Science 2023; 13(4): 351–362. https://doi.org/10.4236/aces.2023.134024
4. Censi R, Di Martino, P. Polymorph Impact on the Bioavailability and Stability of Poorly Soluble Drugs. Molecules 2015; 20(10): 18759–18776. https://doi.org/10.3390%2Fmolecules201018759
5. Kanaujia P, Poovizhi P, Ng WK, Tan RBH. Amorphous formulations for dissolution and bioavailability enhancement of poorly soluble APIs. Powder Technology 2015; 258: 2–15. https://doi.org/10.1016/j.powtec.2015.05.012
6. Thayyil RA, Juturu T, Nayak S, Kamath S. Pharmaceutical Co-Crystallization: Regulatory Aspects, Design, Characterization, and Applications. Advanced Pharmaceutical Bulletin 2020; 10(2): 203–212.

https://doi.org/10.34172%2Fapb.2020.024
7. Bhujbal SV, Mitra B, Jain U, et al. Pharmaceutical amorphous solid dispersion: A review of manufacturing strategies. Acta Pharmaceutica Sinica B 2021; 11(8): 2505–2536. https://doi.org/10.1016%2Fj.apsb.2021.05.014
8. Pardhi V, Lanke TV. Nanocrystals: An Overview of Fabrication, Characterization and Therapeutic Applications in Drug Delivery. Current Pharmaceutical Design 2019; 25(43): 5129–5146. http://dx.doi.org/10.2174/1381612825666190215121148
9. Dunny E, O'Connor I, Bones J. Containment challenges in HPAPI manufacture for ADC generation. Drug Discovery Today 2017; 22(6): 947–951. https://doi.org/10.1016/j.drudis.2017.02.003
10. Bechtold-Peters K, Ruggiero A, Vriezen N. CMC Regulatory Considerations for Antibody-Drug Conjugates. Journal of Pharmaceutical Sciences 2023; 112(12): 2965–2980. https://doi.org/10.1016/j.xphs.2023.09.007
11. Wagh A, Song H, Zeng M, et al. Challenges and new frontiers in analytical characterization of antibody-drug conjugates. MAbs 2018; 10(2): 222–243. https://doi.org/10.1080%2F19420862.2017.1412025.

BIOGRAPHY

Dr. Rohtash Kumar joined Veranova as SVP, Development Operations and Chief Technical Officer in May 2023. He brings deep experience in the CDMO industry, leading technical teams engaged in the discovery and development of new products for use in clinical trials, as well as successfully running programs for commercial supply of APIs in the branded market. Prior to joining Veranova, he served as Site Head at Bachem Americas Inc., where he worked for 8 years holding different positions including VP of API Manufacturing. Prior to Bachem, he worked with Sigma-Aldrich as Manager of R&D and Manufacturing. In the early part of his career, Rohtash worked at Toronto Research Chemicals as a Group Leader, and at Apotex as Senior Research Scientist. He earned his PhD in Organic Chemistry from Delhi University, and an MBA – Production Management from Chaudhary Charan Singh University. He completed post-doctoral work at the University of Alberta, and at the National Research Council of Canada.

NEW PRODUCT INTRODUCTION

Addressing the Pitfalls of Progressing From Pilot to Product Through Effective New Product Introduction

By: Uwe Hanenberg, PhD, Wolfram Bühler, and Radoslaw Kaczanowski, PhD

INTRODUCTION

Introducing a new pharmaceutical product - new production introduction (NPI) - involves transforming an approved product into a refined product ready for clinical trials or commercialization. It is the cornerstone of successful product development and tech transfer of marketed products.

Whether introducing a completely new product, reformulating an existing formulation, or changing the process or equipment of an existing product, having an effective NPI strategy is crucial to avoid challenges stemming from miscommunication, poor knowledge transfer, or elsewhere. Inadequate planning increases the risk of quality issues during the scale-up of new production processes. Addressing this issue can be costly and time-consuming, delaying project progress.

The following explores the risks and challenges pharmaceutical companies face when undertaking NPI to ensure new products successfully reach the market and patients. It also examines the strategies contract development manufacturing organizations (CDMOs) are adopting to ensure the smooth delivery of these projects from discovery to commercialization.

AN INCREASING RELIANCE ON CDMOS WITH NPI EXPERTISE

Offering potential benefits, including capacity, cost efficiency, access to specialized expertise, and global reach, the pharma industry continues to rely heavily on CDMOs to deliver critical medicines to patients with certainty. This is reflected in the expanding global CDMO market, which was valued at around USD $155.7 billion in 2023 and is expected to grow to USD $291.1 billion by 2032, with a compound annual growth rate (CAGR) of roughly 7.20%.[1]

An integral part of the success of these partnerships is the CDMO's NPI experience and expertise. Consisting of managing the design and manufacturing of new therapeutics, NPI forms the basis and foundation of success for any commercial or clinical supply project. It is the process of taking an idea for a novel pharmaceutical product from a working prototype to a refined product ready for clinical trial or commercialisation. As a comprehensive process, it involves a series of stages, including design, development, testing, production, and market launch, encompassing both product development and technology transfer.

UNDERSTANDING THE COMPLEXITIES OF NEW PRODUCTION INTRODUCTION

Due to the complexity of product development and technology transfer, delivering innovations from pilot to product can come with several key considerations that must be navigated to ensure NPI success:

Communication is Important

As the project progresses from discovery to pilot to product, communication between each team is critical. Without effective collaboration between teams, siloed working can result in misunderstandings, errors, and delays, potentially impacting product quality and project success. The teams must organize and attend regular meetings to ensure projects remain on track and any risks are quickly identified and mitigated.

Comprehensive Knowledge Transfer is Vital

When a CDMO partner begins supporting a project, development is typically already underway, with customers having a prototype or pre-developed formulation. In the case of tech transfer, the product is often already established.

In these situations, the knowledge related to the products needs to be transferred efficiently and accurately. This could include sharing a detailed technology transfer plan, comprehensive manufacturing descriptions, and technical gap analysis documents. Without access to this information, the CDMO might risk forming the wrong conclusion or will need to spend time and resources repeating the research and development to attain this information.

Preventing these risks relies on strong communication between all parties, ensuring a clear definition of the scope of work, and ensuring those involved are aware of the quality project plan (QPP) before project initiation.

Robust Regulatory Strategies are Necessary

A well-defined regulatory strategy is needed to ensure compliance with relevant regulations, guidelines, and standards. It also guides the compilation of necessary data, documentation, and validation information required for the submission of regulatory documents, such as drug master files (DMFs) and marketing authorization applications (MAAs).

A clear understanding of the regulatory strategy is required throughout product and process development and tech transfer to ensure compliance and mitigate risk. This involves defining the activities needed to demonstrate stability and validation, going hand in hand with defining the QPP and scope of work.

Steps Must be Taken to Ensure Equipment is Like-to-Like

Another common challenge that can impact the success of tech transfer to a CDMO if not carefully navigated is the transfer of processes to equipment that is not like-to-like, for example, if a process is moved from one model of a granulator to another. As a result, process parameters may require adaptation. Process modeling is essential in these circumstances to make sure that even when changing equipment, the process will be run within a defined design space, ensuring accurate and reliable manufacturing.

Inadequate planning increases the risk of quality issues. This is particularly true during the scale-up of new production processes, as pilot-stage equipment may not be compatible with clinical or commercial manufacturing capacity. Addressing this issue can be costly and time-consuming, delaying project progress.

Standard Processes Must be Maintained

Without a project management strategy that follows a standardized process, drug developers and manufacturers cannot expect to keep to timelines and secure success throughout product development and tech transfer.

A structured NPI process relies on having a project management workbook, risk assessments, transparent communication, and collaboration between teams (particularly with governance teams), and stage gating. Having a stage gate process means drug developers and manufacturers can stop during certain tech transfer or development stages to ensure the necessary objectives, activities, and deliverables are met before moving forward. This helps to manage risk, ensure quality, and streamline the transition from one phase to the next.

With the assistance of CDMOs, pharma companies can prevent quality issues, eliminate risks, and have production processes that are scalable from the outset, enabling a seamless journey as the project moves from discovery to commercialization. However, to achieve this, the CDMO needs to apply the right NPI strategy.

STRATEGIES TO DELIVER WITH CERTAINTY THROUGHOUT NPI

To minimize these risks and overcome the challenges of NPI, drug developers must ensure their chosen CDMO partner has a comprehensive and effective plan in

place. Effective communication between teams throughout the project's journey is vital, as is comprehensive technology transfer support to share knowledge and expertise at each stage.

When selecting a CDMO to support NPI, drug developers should carefully consider if their potential partner can offer the following factors needed to secure success:

Applying a Science-led Approach to Ensure Effective NPI

A science-led approach to decision-making is integral to the success of tech transfer and product development, relying on the design of experiments (DoE) and quality by design (QbD) (based on risk assessment and available data) while leveraging statistical tools and modeling. DoE is a powerful tool to optimize formulations and processes, minimizing drug development risks at the earliest stage of the NPI process and enhancing efficiency during scale-up from bench to clinic to commercial. As a result, quality is built in from the beginning and helps to ensure that products meet their quality target product profile (QTPP). A CDMO backed by a dedicated network of scientists can provide vital support in delivering in this area.

When applying a fact-based approach from the start of the product development or tech transfer project, the CDMO must evaluate all the processes and materials. This includes examining the critical process parameters (CPPs) and material attributes to gain a greater understanding of how they are related to the quality attributes. A supporting risk assessment can further help developers and manufacturers identify the critical parameters of the process and quality attributes.

The CDMO can leverage a statistically supported trial design to confirm the critical parameters and attributes identified. Consequently, those then will be used to define the design space. The knowledge obtained from the trials can be used when upscaling to determine the best process for commercial production independent of the used equipment size or type.

A structured project management process and a scientific approach based on DoE principles, help assess and address risks and identify and quantify the influence of critical parameters. With this approach, the CDMO can have a prototype formula suitable for the desired manufacturing process after 1-2 days, consuming only a small amount of API.

An Example: A Science-led Approach to OSD Manufacturing: In oral solid dose (OSD) manufacturing, tablet, capsule, and granular formats require powder with suitable flowability. A powder's flowability will consist of a two-digit number of different impact parameters, including particle size, particle shape, loss on drying, porosity, and density. It is critical to investigate the quantitative impact of these parameters flowability of the powder.

Within a powder characterization lab, CDMOs can measure the different parameters in a scientific-approach trial design using a few grams of active pharmaceutical ingredient (API) to identify the critical components impacting flowability. From an excipient database, the CDMO can then select suitable excipients to enhance flowability and use this to design the formulation in silico. The formulation can then be blended for prognosis to verify the improvement in flowability, with the CDMO iteratively changing the formula based on the measurements to maximize the success rate.

Global Project Management

To standardize tech transfer processes and increase efficiency, global CDMOs with multiple locations to support customers must consider implementing a project management organization with harmonized rules and structure. Working with the local teams, the global project management organization can provide state-of-the-art tech transfer processes applied with rigor and discipline. The project should follow a structured yet malleable development process of continuous monitoring and rigorous controls to deliver efficacious and safe therapeutics at speed.

Efficiency & Resource Leverage

By leveraging resources across the organization, CDMOs can minimize hands-on time and ensure projects can be completed more quickly and effectively. With a scientific network that is efficient and adept at transitioning between facilities with a clearly defined handover, the right CDMO partner can minimize delays by guaranteeing the prompt communication of knowledge to the right expert at the right time. This can drive time and cost savings for drug developers, helping to deliver critical therapies to patients sooner.

Experience

CDMOs with a long history of performing tech-transfer between their sites as well as to and from third parties will understand how to scale up, tech-transfer, and validate processes rapidly with a focus on product quality. A strong track record of smooth tech transfers can provide drug developers with the confidence that their CDMO partner will onboard their small and large molecule projects seamlessly.

Comprehensive Support

By supporting all aspects of the tech-transfer process, from consideration of the equipment available at the new site and understanding critical process parameters, to handover of manufacturing and quality control methods, CDMOs can ensure the transfer process is as smooth and seamless as possible.

Forming the foundation for the success of any product development or tech transfer, CDMOs must also be able to support technology and scale, offering all the technologies in small, pilot, and full scale.

Transparency

Complete transparency is critical during the tech transfer process. All process documentation, including successful runs and any failures or issues, must be made fully transparent between parties to ensure complete information transfer. This relies on clear and frequent communication between parties and teams.

Harnessing effective communication, collaboration, and process management, the right CDMO can scale, transfer, and validate processes rapidly while mitigating risks and complying with stringent regulations.

UNLOCKING THE SECRETS TO EFFECTIVE NPI IN THE FUTURE

As increasing numbers of pharma companies seek partnerships with CDMOs in the future to alleviate needs for capacity, expertise, and global access, drug developers must carefully consider whether their prospective partners can deliver NPI success. Effectively navigating the complexities of NPI requires careful planning, open communication, and robust project management. By partnering with a CDMO that applies a fact-based approach, has a global project management organization, and offers comprehensive support, pharmaceutical companies can overcome the challenges of NPI and bring their products to the market with certainty. ◆

REFERENCE

1. https://www.zionmarketresearch.com/report/pharmaceutical-cdmo-market

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OXYGEN SCAVENGING

Innovative Oxygen Scavenging Technologies for Pharmaceutical Packaging: Ensuring Drug Integrity and Stability

By: Amanda Murph, Ivy Comer, Jason Pratt, PhD, and Jean Daou, PhD

ABSTRACT

Oxygen scavenging is a vital strategy in pharmaceutical packaging, aimed at preventing the oxidation and degradation of drugs. By incorporating novel active materials science technology into active packaging solutions to actively remove oxygen from the packaging headspace, pharma companies can ensure the stability and efficacy of products throughout shelf-life. Sophisticated oxygen scavenging technology can be seamlessly integrated into existing packaging formats and processes as pieces of film (heat-staked films, blown films, etc), minimizing disruption to manufacturing workflows.

INTRODUCTION

Oxygen scavenging in food and pharmaceutical packaging is a critical technology designed to enhance the stability and shelf-life of various drug and food products.[1,2] Oxygen, even in trace amounts, can lead to the oxidation and subsequent degradation of active pharmaceutical ingredients (APIs), impacting their efficacy, safety, and appearance. The oxidation process can cause the formation of harmful by-products, reduce the potency of APIs, and alter physical characteristics, such as color and solubility. Consequently, controlling and minimizing oxygen levels within pharmaceutical packaging is paramount to maintaining drug quality. The application of oxygen scavenging technology is especially important for those pharmaceuticals particularly sensitive to oxidation, such as certain antibiotics, vitamins, and biologics. Notably, the use of oxygen scavengers can reduce the need for preservatives and antioxidants within the formulation, potentially lowering risk of adverse reactions.

Varying strategies can be used to address risks initiated by the presence of oxygen inside the packaging headspace.[3] Common methods used to mitigate oxygen in packaging include the following:

Barrier Materials: Packaging with high oxygen barrier properties can be used to prevent external oxygen from entering the package.[4]

Modified Atmosphere Packaging (MAP): In MAP, the atmosphere inside the package is adjusted by replacing oxygen with inert gases (eg, nitrogen, carbon dioxide).[5]

Chemical Scavengers: These include organic scavengers (ascorbic acid, ascorbic acid salts, isoascorbic acid, tocopherol, hydroquinone, catechol, rongalite, sorbose, lignin, gallic acid, lecithin, rosemary extracts, polyunsaturated fatty acids, threonine), metallic scavengers (iron powder, activated iron, ferrous oxide, iron salt, iron nanoparticles, Co (II), Zn, platinum, palladium), inorganic (non-metallic) scavengers (sulfite, thiosulfate, dithionite, hydrogen sulfite, titanium dioxide) and polymer based scavengers (oxidation-reduction resin, polymer metallic complex).[6-8]

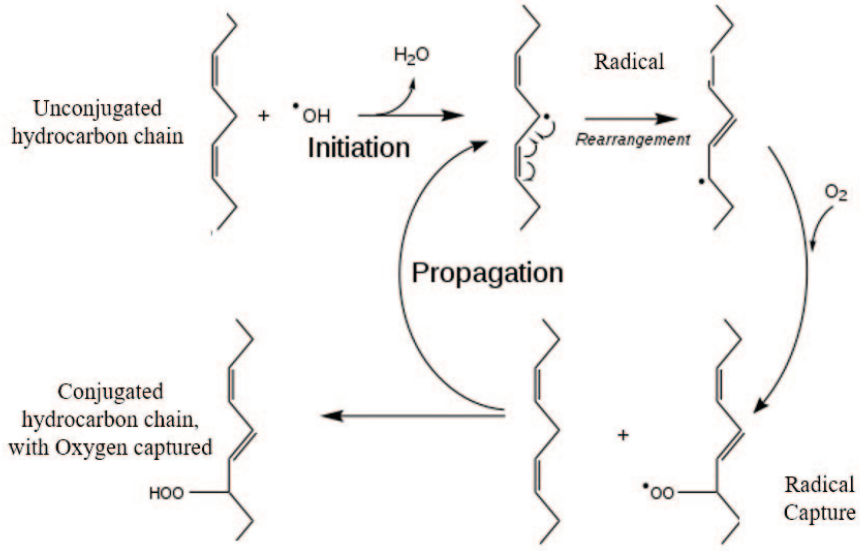
Enzymatic Scavengers: The most prominent are glucose oxidase, laccase, and ethanol oxidase. Enzymes like glucose oxidase catalyze the conversion of glucose to gluconic acid and hydrogen peroxide. The latter reacts with oxygen, reducing its levels.[9]

The first two strategies (barrier materials and modified atmosphere packaging) can be utilized to protect unit dose (individual) drug packaging, but are inefficient for packaging containing several doses because external oxygen can enter the packaging as the user repeatedly opens and closes it. One widely used solution is oxygen scavenging materials, which can be incorporated into packaging systems to protect sensitive products by actively removing oxygen from the surrounding environment. These scavengers can be integrated into various components of the packaging, such as bottle closures, blister packs, or sachets, and operate through chemical reactions that absorb or adsorb oxygen. Commonly used oxygen scavenging materials include iron powder and ascorbic acid, either of which is chosen based on the specific requirements of the drug product and packaging design.

Iron-based scavengers work through a process of oxidation where iron reacts with oxygen to form iron oxide, effectively reducing oxygen concentration.[6] Ascorbic acid, another widely used scavenger, reacts with oxygen to form dehydroascorbic acid. Non-metallic scavengers can also be a solution when metallic systems are not permitted. Among these, sulfites are highly effective oxidation compounds.[10]

An alternate technology, not requiring water, that produces peroxyl radicals and ultimately acts as an oxygen scavenger has also been of interest. In this technology, peroxyl radicals arise from the direct interaction between oxygen and alkyl radicals. The formation of peroxyl radicals are limited to the oxygen available in the headspace in a sealed package. An unconjugated chain reacts with the peroxyl radicals to capture the oxygen. The bonds then rearrange to form an oxygen-bound conjugated chain. Figure 1 depicts this reaction. Depending on the length of the chain, multiple oxygen molecules could be captured. Once the oxygen is bound to the hydrocarbon chain, the compound is very stable. These types of scavengers can be modified with photo initiators to prevent premature oxidation of the scavenger during processing. Enzyme-based oxidation is another approach to regulating the oxygen concentration in food packages. Enzymatic scavengers employ enzymes to catalyze reactions that convert oxygen into less reactive species. These materials are often selected based on their compatibility with food and drug products, the desired rate of oxygen removal, and regulatory considerations. Some of them can start scavenging oxygen immediately after exposure to oxygen or air at ambient humidity and temperature. On the other hand, some oxygen scavengers require an activation mechanism (water vapor, ultra-violet light or magnetic fields, for example), that helps control the initiation of the reaction, allowing the oxygen scavenging system to be stable before use with drugs and avoiding its premature activation.

FIGURE 1



Peroxyl Radical Based Oxygen Scavenger Reaction.

The following explores how chemical oxygen scavengers can be deployed using a novel active polymer platform to scavenge oxygen. Such an approach can substantially limit the amount of oxygen in the packaging headspace that could otherwise cause deteriorative reactions and, ultimately, lead to reduced drug functionality.

METHODS

Pioneered by Aptar CSP Technologies, the 3-Phase Activ-Polymer™ platform technology employs active materials as fillers in composite materials (Figure 2). The proprietary technology is delivered in a unique formulation comprised of a base

majority polymer that provides the structure, a channeling agent, and active particles. In this case, the polymer was deployed as an active film.

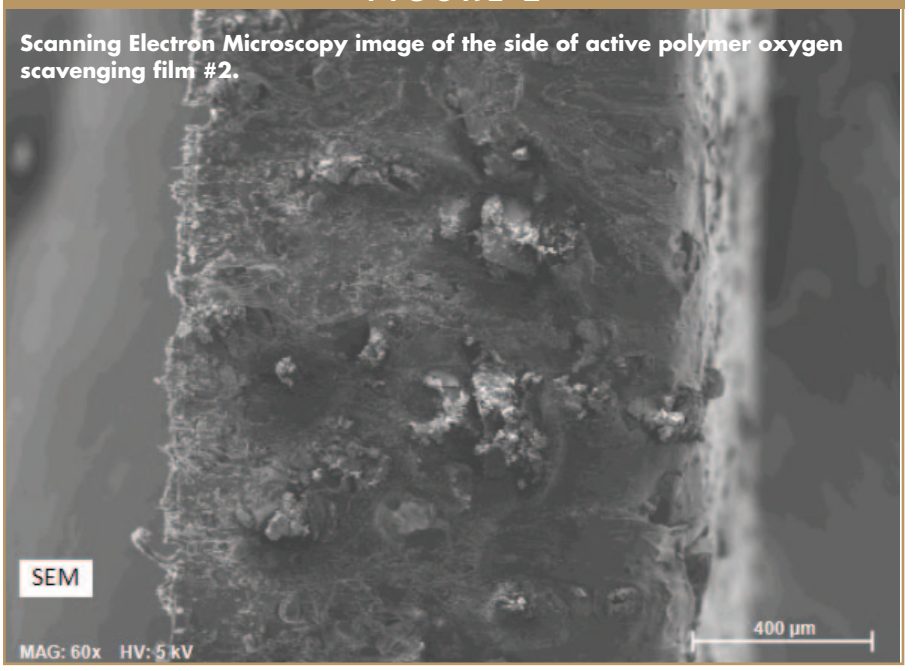
As a first step, five different raw active chemical oxygen scavengers (three using humidity as a trigger to scavenge oxygen, and two that work in dry conditions) and one enzymatic scavenger were engineered for inclusion into a polymer matrix (Figure 3). The incorporation of oxygen scavenging systems into the polymer matrix may affect the functional properties of the plastic, including the tensile strength, elongation, gas barrier, thermal properties, and optics. Therefore, the chemical and physical compatibility with the scavenger, as well as the stability with the active phase during the manufacturing processes, were considered when developing the oxygen scavenging films. A good dispersion of the scavenging agent by sufficient shear during the extrusion process was also achieved, as shown from the homogeneity of the dispersion of the active materials in the polymer matrix of oxygen scavenging film #2 (Figure 2).

Twelve glass bottles (V = 120 mL) were cleaned and prepared with oxydot, and a 1 x 1 in^2 piece of one of six different active films was placed in the bottle (two bottles per each type of film) (Figure 3). For the wet oxygen scavenging system, a 1 x 1 in^2 filter paper impregnated with a certain volume of water (Table 1) was also added to the bottle.

The bottles were then crimp sealed and analyzed by the OxySense system (Gen III, 5000 series) for an initial oxygen reading before being stored in a 25^{0}C/ 60% RH environmental chamber. Using the OxySense system, two samples of each type of the six films (Figure 3) were tested daily for 200 days.

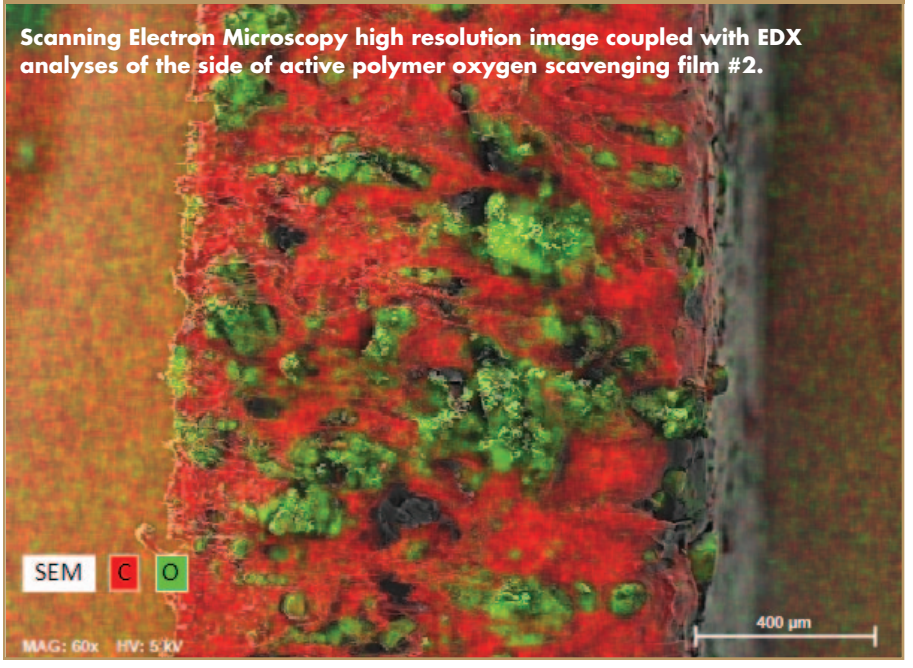
OxySense uses a luminescence method to calculate the amount of oxygen in a closed system. Oxygen absorption rate (OAR) tests were executed for both the wet and dry oxygen scavenging films (Table 1). Once the OAR data was collected, the percent change of oxygen in each bottle was calculated by subtracting the final percentage of oxygen in the bottle from the initial percentage. The amount of oxygen present in the bottle was calculated by multiplying the volume of the bottle (120 mL) by the percentage change of oxygen. Then, the OAR was calculated by dividing the amount of oxygen present by elapsed time.

FIGURE 2



Scanning Electron Microscopy image of the side of active polymer oxygen scavenging film #2.

FIGURE 3



Scanning Electron Microscopy high resolution image coupled with EDX analyses of the side of active polymer oxygen scavenging film #2.

RESULTS & DISCUSSION

Figure 4 shows the OAR for the other six oxygen scavenging films for the full 200 days.

O_2 Film #5 and O_2 Film #6, which can react with oxygen in the absence of humidity, show the highest OAR value among the films that can be used for 200 days. O_2 Film #5 displayed an OAR of 0.060 cc/day. O_2 Film #6 displayed the highest OAR value of 0.073 cc/day, 0.013 cc/day higher than O_2 Film #5.

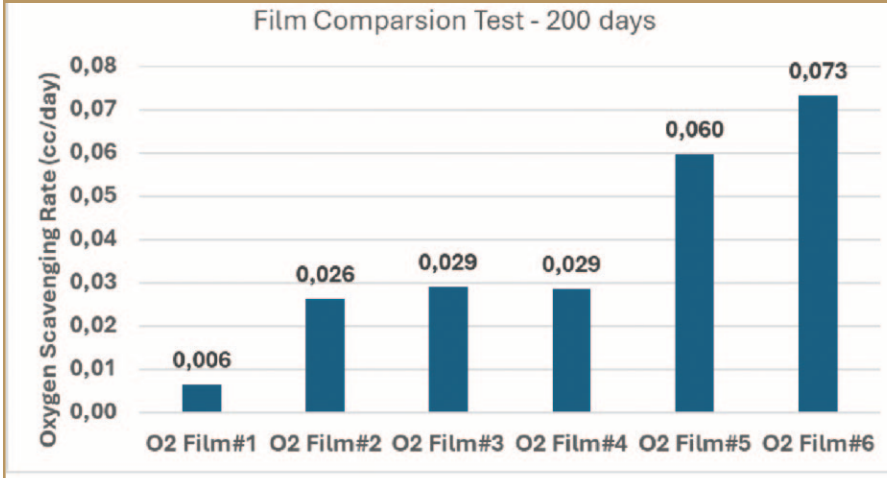
The capacity of the films was then calculated after the full data set was collected. First, the amount of oxygen left in the bottle was calculated by multiplying 120 mL by the minimum oxygen reading in the data set. Next, the amount of oxygen scavenged was determined by subtracting the oxygen left in the bottle from the original amount of oxygen in the bottle, which was assumed to be 21% oxygen. Then, the capacity was calculated by dividing the amount of oxygen scavenged by the surface area of the sample, which was 1 in^2 or 6.45 cm^2. Figure 5 below shows the capacities of the films tested.

The capacity calculated for O_2 Film #5 is 2.19 cm^3/cm^2, which is higher than most of the other films tested. The capacity calculated for O_2 Film #6 was the highest (2.60 cm^3/cm^2), which is 16% higher than O_2 Film #5.

TABLE 1

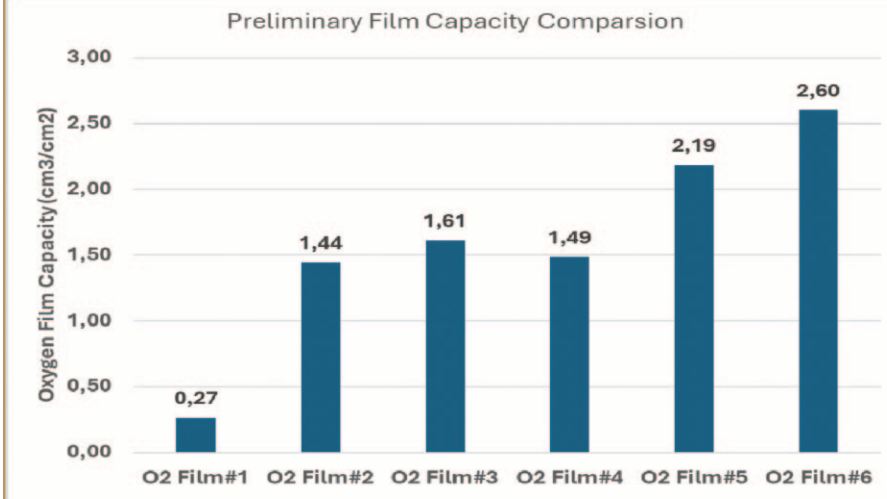
Film Code	Set Up Used	Scavenger Type
O2 Film #1	Wet – 1.0 mL	Chemical
O2 Film #2	Wet – 0.5 mL	Chemical
O2 Film#3	Wet – 0.5 mL	Enzymatic
O2 Film #4	Wet – 0.5 mL	Chemical
O2 Film #5	Dry	Chemical
O2 Film #6	Dry	Chemical

FIGURE 4



OAR for O_2 Film#1, O_2 Film#2, O_2 Film#3, O_2 Film #4, O_2 Film #5, and O_2 Film #6.

FIGURE 5



Film Capacities for all Prepared Films

CONCLUSION

Oxygen scavengers will continue to play a crucial role in pharmaceutical packaging by protecting drugs from oxidative degradation. As manufacturers seek to optimize costs and maintain drug potency, these scavengers help extend shelf life and prevent adverse effects caused by oxygen exposure. Incorporating scavengers directly into packaging can help pharma developers mitigate degradation risk, enhance stability, and meet regulatory requirements without the need to reformulate their drugs.

Aptar CSP Technologies' novel 3-Phase Activ-Polymer™ oxygen scavenging films, which actively remove oxygen from packaging headspace, can significantly extend the shelf life of drugs subjected to

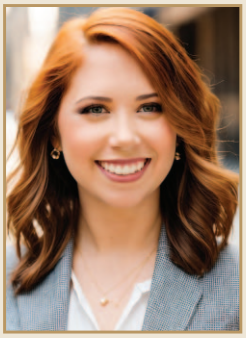
oxidative degradation, ensuring they remain effective until the end of their intended use. ◆

REFERENCES

1. Apicella, A., Incarnato, L., Oxygen Scavengers in Food Packaging, Reference Module in Food Science, Elsevier, 2019, ISBN 9780081005965.
2. Dey, A., Neogi, S., Oxygen scavengers for food packaging applications: A review. Trends in Food Science & Technology, 2019, 90, 26-4.
3. Gaikwad, K.K., Singh, S., Lee, Y.S., 2018. Oxygen scavenging films in food packaging. Environ. Chem. Lett., 16, 523–538.
4. Zabihzadeh Khajavi, M., Ebrahimi, A., Yousefi, M. et al., Strategies for Producing Improved Oxygen Barrier Materials Appropriate for the Food Packaging Sector. Food Eng. Rev., 2020, 12, 346-363.
5. Han, J.H., A review of food packaging technologies and innovations, Innovations in food packaging (second edition). Academic Press, 2014, 3-12.
6. Johansson, K., Jönsson, L., Järnström, L., 2011. Oxygen scavenging enzymes in coatings – effect of coating procedures on enzyme activity. Nord. Pulp Pap. Res. J., 26, 197-204
7. Miltz, J., Perry, M., Evaluation of the performance of iron-based oxygen scavengers, with comments on their optimal applications. Packag. Technol. Sci., 2005, 18, 21-27.
8. Damaj, Z., Joly, C., Guillon, E., 2015. Toward new polymeric oxygen scavenging systems: formation of poly(vinyl alcohol) oxygen scavenger film. Packag. Technol. Sci., 28, 293-302.
9. Scarfato, P., Avallone, E., Galdi, M.R., Di Maio, L., Incarnato, L., Preparation, characterization, and oxygen scavenging capacity of biodegradable a-tocopherol/PLA microparticles for active food packaging applications. Polym. Compos., 2015, 38, 981-986.
10. Brody, A.L., Strupinsky, E.P., Kline, L.R., Active Food Packaging for Food Applications. CRC Press, Boca Raton, FL, 2001.

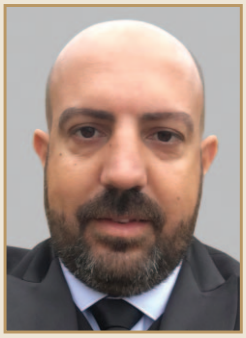
BIOGRAPHIES

Amanda Murph is a Scientist II in the Research and Applications Development division at Aptar CSP Technologies. With a Bachelor's degree in Materials Engineering, she demonstrates a strong commitment to innovation and collaborative problem-solving by consistently exploring novel material applications and focusing on achieving tangible results.



Ivy Comer, a Scientist III in the Applications and Research Development Team at Aptar CSP Technologies, holds a Bachelor of Science in Biochemistry from Auburn University. Her expertise in innovation, analytical methodologies, and strategic problem-solving has driven impactful solutions in the medical and packaging industries.

Jason D. Pratt is Director of Material Science at Aptar CSP Technologies with a passion for bringing innovative solutions to commercial opportunities. Skilled at bringing together and mentoring high power teams to tackle impossible problems, he is a green chemist with over 40 patents across the food, cosmetics, pharma and construction industries.



Dr. Jean Daou, after earning a PhD in Material Chemistry from the University of Louis Pasteur, joined the University of Haute Alsace as Assistant Professor and was promoted to full professor in 2016. In 2021, he joined Aptar CSP Technologies as R&D Manager, where his research activities focus on the synthesis of porous materials, the study of their properties and their shaping to meet pharmaceutical packaging demands for molecular decontamination. He is the author of 137 publications in international journals and 18 patents.

FOCUSED ULTRASOUND

Overcoming Drug Delivery Challenges

By: Neal F. Kassell, MD

INTRODUCTION

Research scientists and biopharmaceutical companies continue to push the boundaries of medicine, developing treatments that offer new hope to patients with various complex conditions. Innovations like gene therapy have shown the potential to reverse genetic disorders, CAR-T therapies have enabled the immune system to target and eliminate cancer cells, and advanced HIV medications have rendered the virus virtually undetectable. In addition to these approved treatments, industry pipelines hold thousands of development candidates aimed at transforming patient care in diverse therapeutic areas.

However, some diseases remain formidable, defying even the most advanced therapies. Among these challenging conditions, glioblastoma and neurodegenerative diseases like Alzheimer's disease present particularly high hurdles; the drug development failure rate in Alzheimer's exceeds 98%. Many drug candidates designed to treat neurodegenerative diseases and brain cancer fail due to the blood-brain barrier (BBB), a tightly knit endothelial cell structure along the blood vessels that prevents potentially harmful substances from entering the brain but also restricts therapeutic molecules from reaching their targets.

The challenge of the BBB has spurred a wave of innovation, with scientists seeking new ways to circumvent this protective mechanism to deliver drugs effectively. One promising approach, focused ultrasound (FUS), is emerging as a revolutionary tool, enabling non-invasive, targeted BBB disruption. This method holds transformative potential in delivering therapies for neurodegenerative diseases and other challenging conditions, setting the stage for novel treatments in the years ahead.

FOCUSED ULTRASOUND: A NEW FRONTIER IN MEDICINE

Focused ultrasound uses ultrasonic energy to precisely target deep tissues without incisions, radiation, or significant side effects and can treat tissue using a variety of desired biological effects. Cleared by the US FDA, focused ultrasound ablation can treat conditions like essential tremor, Parkinson's disease, prostate cancer, uterine fibroids, liver tumors, and pain from bone metastases. It is being explored globally in dozens of medical indications and has more than 30 regulatory approvals worldwide. By combining ultrasound and imaging technologies, FUS enables real-time monitoring, allowing clinicians to guide and adjust treatments accurately.

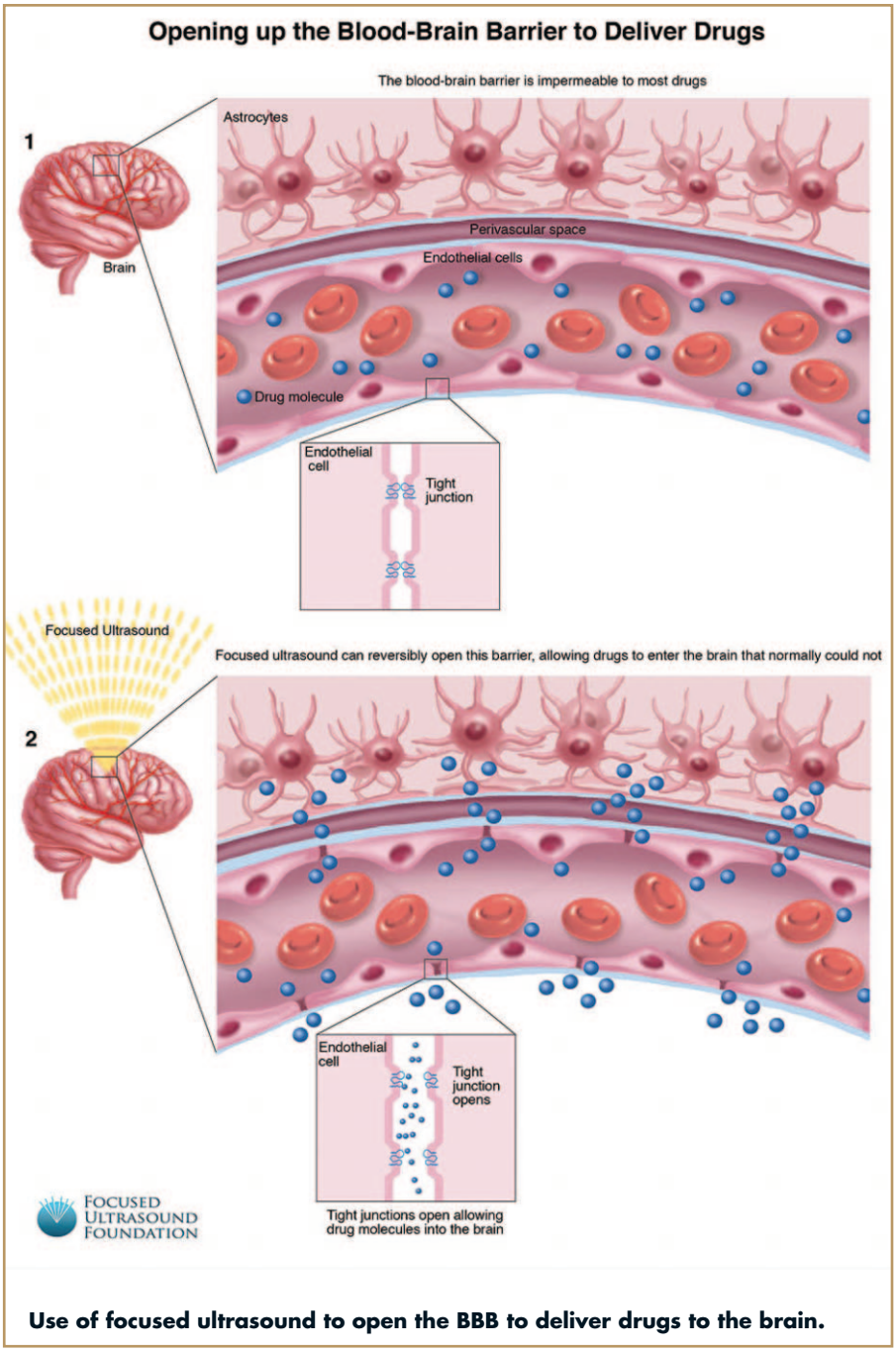
Focused ultrasound is the marriage of two innovative technologies:

Focused Ultrasound: provides the energy to treat tissue deep with high precision and no incisions.

Magnetic Resonance or Ultrasound Imaging: used to identify and target the tissue to be treated, guide and control the treatment in real-time, and confirm the effectiveness of the treatment.

The fundamental principle is analogous to using a magnifying glass to focus beams of sunlight on a single point to burn a hole in a leaf. With focused ultrasound, an acoustic lens is used to concentrate multiple intersecting beams of ultrasound on a target deep in the body with extreme precision and accuracy.

Where each of the individual beams passes through the tissue, there is no effect. But, at the focal point, the convergence of the multiple beams of focused ultrasound energy results in many



Use of focused ultrasound to open the BBB to deliver drugs to the brain.

important biological effects, creating the possibility of treating a variety of medical disorders.

One of the most promising applications of FUS lies in its capacity to temporarily and safely disrupt the BBB. The technique involves injecting microbubbles, used in the clinic as ultrasound contrast agents, into the bloodstream. When ultrasound waves are directed at the targeted brain regions, these bubbles oscillate, creating mechanical forces that temporarily push apart the endothelial cells of the BBB. The resulting temporary increase in BBB permeability can last 24 to 48 hours, during which larger therapeutic molecules (previously unable to cross the barrier) can reach their intended targets. This advancement has major implications for treating Alzheimer's isease, Parkinson's disease, amyotrophic lateral sclerosis (ALS), and brain tumors.

FOCUSED ULTRASOUND IN ALZHEIMER'S RESEARCH

The potential of FUS in Alzheimer's disease treatment is supported by groundbreaking studies, including one that demonstrated the ability of the technology to safely and reversibly open the BBB in Alzheimer's patients, specifically targeting areas of the frontal lobe where amyloid plaques are concentrated.[1] Subsequent studies confirmed these results, showing not only successful BBB disruption but also measurable decreases in amyloid levels post-treatment.[2]

Recently, a team at West Virginia University's Rockefeller Neuroscience Institute used FUS to improve the delivery of aducanumab, an anti-amyloid drug for Alzheimer's disease initially approved in 2021.[3] Using MRI-guided focused ultrasound directed to specific brain regions, they achieved targeted BBB opening, allowing higher concentrations of aducanumab to enter the brain. PET scans confirmed that the side of the brain treated with FUS had a significant reduction in amyloid plaques compared to the untreated areas, highlighting the approach's potential to accelerate plaque clearance due to enhanced drug delivery with FUS BBB opening.

While aducanumab was recently removed from the market due to efficacy concerns, this study now continues with Lecanemab. Ongoing research is exploring FUS-assisted BBB opening in combination with other anti-amyloid drugs, seeking alternative treatment pathways for Alzheimer's disease patients.

Magnetic resonance imaging is used to identify and target the tissue to be treated and guide the opening of the BBB.

EXPANDING THE REACH OF FOCUSED ULTRASOUND IN ONCOLOGY

Oncology is also a major area of interest for researchers exploring the use of FUS, with clinical trials examining the potential to enhance drug delivery for brain tumors, such as glioblastoma (GBM). GBM is the most common glioma and occurs in 3 per 100,000 people annually in developed countries, is not curable, and has a grim prognosis (a 5-year survival rate of less than 10%) that has remained unchanged for more than 30 years.

These aggressive cancers often resist traditional therapies, partly due to the BBB's role in blocking chemotherapeutics. By transiently disrupting the BBB, FUS could allow chemotherapy drugs to more effectively reach tumor cells, potentially improving patient outcomes. Preliminary studies have shown promising results, paving the way for larger clinical trials.

A team of French researchers recently conducted a comprehensive review of preclinical and clinical studies to summarize the varying approaches of using focused ultrasound to deliver anticancer drugs across the BBB and blood-tumor barriers for the treatment of glioma.[4]

The team analyzed 60 published studies (51 preclinical and 9 clinical trials). Among these, there were 29 that delivered free drugs (22/29 preclinical), 22 that employed drug-loaded nanoparticles (20/22 preclinical), and 9 that used drug-loaded microbubbles (all preclinical). Both large- and small-molecule anticancer agents have been delivered, including conventional chemotherapies, monoclonal antibodies, immunotherapies, and modified cell-based therapies. These various therapies were introduced via intravenous bolus, intravenous infusion, intraperitoneal injection, orally, intranasally, or intra-gastrically. At the time of publication, 13 GBM additional clinical trials were ongoing.

Through these studies, the safety and feasibility of using focused ultrasound BBB disruption (FUS-BBBD) has been established for different FUS devices, repeated sessions, and different chemotherapies in patients with newly diagnosed GBM, recurrent GBM, and high-grade gliomas.

The authors found that using focused ultrasound for BBBD improved the intracerebral concentration of anticancer therapies in both healthy brains (a 1.4- to 16.6-fold increase) and in glioma models (a 1.6- to 8-fold increase) compared with the non-sonicated contralateral hemisphere. In glioma models, focused ultrasound increased the delivery of the therapeutic agents in the healthy contralateral hemisphere, averaging 4.2-fold for small molecules and small targeted therapies, and 3.6-fold for larger monoclonal antibodies. Furthermore, transient focused ultrasound BBB disruption also improved the concentration of anticancer therapies in brain tumors when compared with non-sonicated tumors (a 1.4- to 13.9-fold increase). As might be expected, this increase was higher for small molecules (5.2-fold) than for monoclonal antibodies (3.7-fold).

TACKLING THE CHALLENGE OF GENE THERAPY DELIVERY

FUS is also being explored to address the challenge of gene therapy delivery.

Designing an effective delivery system that ensures the nucleic acid reaches target cells or tissues without being degraded or causing off-target effects is one of the most critical challenges facing the field of gene therapy. A therapy that can't reach its intended target at a sufficient dose will not succeed, as it could either fail to elicit the desired biological response or, worse, cause unintended consequences in healthy cells. Success in this area is essential to unlock the full potential of gene therapy for treating a wide range of genetic disorders.

Several presentations at the 2023 Focused Ultrasound and Gene Therapy Workshop hosted by the Focused Ultrasound Foundation emphasized that FUS offers a platform to non-invasively increase the delivery efficiency of both viral and non-viral gene therapy vectors.[5] This

could expand therapeutic reach to larger tissue volumes rather than direct injections, with more uniform distribution while requiring lower vector doses that improve safety and manufacturing feasibility. At the workshop, researchers presented data demonstrating the feasibility of targeting diverse brain regions and cell types without overt toxicity. Enhanced delivery of adeno-associated viruses (AAVs), lipid nanoparticles, and other vectors have been shown across animal models.

While FUS can temporarily and reversibly open the BBB for gene therapy delivery using viral vectors, challenges remain in terms of efficiency and specificity. One approach to addressing this is to engineer viral capsids specifically for FUS delivery.6 In one study discussed at the workshop, a library of mutated capsids was injected into transgenic mice, and FUS was applied to one hemisphere. After transduction, the hemispheres were analyzed to identify variants enriched in the FUS-targeted side. This resulted in five capsid candidates that exhibited specific enrichment up to 2.5-fold in the brain; one variant showed over 10X combined improvement in brain targeting.

A PROMISING FUTURE FOR FOCUSED ULTRASOUND

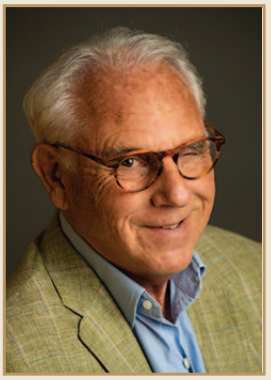
Focused ultrasound is redefining how clinicians approach some of the most challenging diseases, particularly those affecting the brain. The technology's versatility has fueled a wave of new clinical applications, offering potential in disease areas where traditional therapies have fallen short. With its capacity to safely disrupt the BBB, FUS may become a cornerstone in treating neurodegenerative diseases, genetic diseases, and brain cancer, advancing the goals of precision medicine, and providing hope to millions affected by these conditions.

As research progresses, FUS is likely to play a pivotal role in the treatment landscape, not only in neurology but also in cancer and beyond. For drug developers and clinicians, FUS opens new avenues for drug delivery, enabling more effective therapies for diseases that previously seemed beyond reach. This promising technology underscores the power of innovation in medicine, revealing new possibilities for the future of patient care. ◆

REFERENCES

1. Lipsman N, et al. Blood-brain barrier opening in Alzheimer's disease using MR-guided focused ultrasound. Nat Commun. 2018 Jul 25;9(1):2336. doi: 10.1038/s41467-018-04529-6. PMID: 30046032; PMCID: PMC6060168.
2. Chang KW, et al. Blood-Brain Barrier Opening in Magnetic Resonance Images. J Korean Neurosurg Soc. 2023 Mar;66(2):172-182. doi: 10.3340/jkns.2022.0236. Epub 2022 Dec 20. PMID: 36537034; PMCID: PMC10009247.
3. Rezai AR, et al. Ultrasound Blood-Brain Barrier Opening and Aducanumab in Alzheimer's Disease. N Engl J Med. 2024 Jan 4;390(1):55-62. doi: 10.1056/NEJMoa2308719. PMID: 38169490.
4. Bérard C, et al. Anticancer drug delivery by focused ultrasound-mediated blood-brain/tumor barrier disruption for glioma therapy: From benchside to bedside, Pharmacology & Therapeutics. (2023) 250:108518. https://doi.org/10.1016/j.pharmther.
5. 2023 Focused Ultrasound for Gene and Cell Therapy Workshop. https://cdn.fusfoundation.org/2024/05/01084708/Focused-Ultrasound-Foundation-Gene-Therapy-Workshop-White-Paper-2023.pdf.
6. Li H, et al. Engineering Viral Vectors for Acoustically Targeted Gene Delivery. bioRxiv. (2021) doi:10.1101/2021.07.26.453904.

BIOGRAPHY



Neal F. Kassel, MD, is the founder and Chairman of the Focused Ultrasound Foundation and former Co-Chair of Neurosurgery at the University of Virginia. He has published more than 500 scientific papers and book chapters, and his research has been supported by over $30 million in NIH and industry grants and contracts. A member of numerous medical societies in the US and abroad, he has served on many standing and ad hoc committees of the National Institutes of Health and in an editorial capacity for a variety of academic journals. In April 2016, he was named to the Blue Ribbon Panel of then-Vice President Joe Biden's Cancer Moonshot Task Force. He is a founder of numerous private ventures, including Interax, Inc.; the Virginia Neurological Institute; Multimedia Medical Systems, Inc.; the Neuroclinical Trials Center; the NeuroVenture Fund; and MedSpecialists.net. He has served on a number of corporate and not-for-profit boards, including Eclypsis Corporation; INC Research; the Prostate Cancer Foundation; Insightec, Ltd.; the Expedition Trust Company; Tuesday Evening Concert Series and Virginia National Bank. He is currently a Director of the Focused Ultrasound Foundation. He is a shareholder in Insightec, Ltd., where he also served on the board until 2012. He earned his undergraduate and medical education at the University of Pennsylvania.

Technology & Services Showcase

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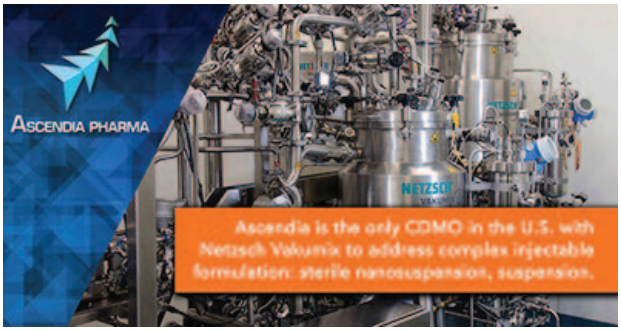
Adare Pharma Solutions is a global technology-driven CDMO providing end-to-end integrated services, from product development through commercial manufacturing and packaging, with expertise in complex oral formulations. Adare's specialized technology platforms provide taste masking, controlled release, 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.**

Manufacturing Facility



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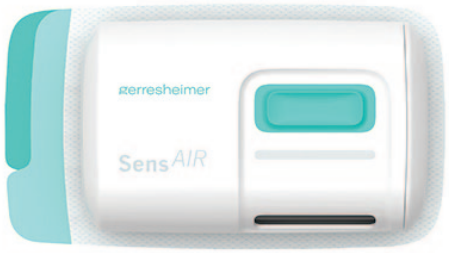
Credence MedSystems is an innovator in drug delivery devices. Credence's philosophy of *Innovation Without Change* results in products that impress and protect end-users while preserving pharma's existing processes, sourcing strategies and preferred primary package components. The Companion® family of syringe systems includes proprietary integrated needle-retraction technology, reuse prevention, critical safety & usability features as well as sustainability advantages. The Dual Chamber platform offers simplified delivery for drugs requiring reconstitution or sequential injection at the time of delivery. The Credence Connect™ Auto-Sensing Injection System incorporates automatic real-time monitoring of critical injection data into a reusable ergonomic finger grip. Credence's Metered Dosing product line allows precise delivery of small volumes and a force advantage when viscosities are high. For more information, call +1 844-263-3797 (+1-844-CMEDSYS), email info@credencemed.com, or visit **www.CredenceMed.com.**

On-Body Drug Delivery



SensAIR is a platform for on-body drug delivery that can deliver drugs of higher viscosity, such as monoclonal antibodies. The aim is to provide patients with the best possible support in the subcutaneous delivery of large-volume biologics. The ready-to-use SensAIR On-Body Delivery Device is easy to use and enables patients to start medication in a self-determined manner in familiar surroundings. The SensAIR On-Body Delivery Device can be adapted to medications of different viscosities and with different requirements. This applies to the size of the medical device as well as to the needle used, variable cartridge sizes and possible connectivity, for example to the patient's smartphone. Together with Gerresheimer's One-Stop-Shop quality promise, which includes a solution from the cartridge to the drug delivery device from a single source, SensAIR enables optimized delivery of biologics. For more information, visit Gerresheimer at **www.gerresheimer.com.**

Technology & Services Showcase

New Isolator Filler Capacity

Lifecore Biomedical is a fully integrated CDMO with differentiated capabilities in the development, fill and finish of sterile injectable pharmaceutical products. Proven capability with complex formulations and highly viscous products (>100,000 cP) highlights our ability to undertake challenges. With 20+ commercial products and a 40+ year regulatory track record, we are deeply knowledgeable on how to efficiently drive programs from clinical to commercial. No matter the size of your organization or the stage of your project, let's explore how Lifecore may be the right HOME for your molecule. For more information, visit Lifecore Biomedical at **www.lifecore.com.**

Global Data & Analytics

PharmaCircle is a leading provider of global data and analysis on the pharmaceutical, biotechnology, and drug delivery industries. PharmaCircle's premier database delivers an integrated scientific, regulatory, and commercial landscape view with unprecedented access to hundreds of company, product, and technology attributes. PharmaCircle connects product and pipeline information for drugs and biologics with formulation and component details, and provides due diligence level data on nearly 6,000 drug delivery technologies and devices. Drug label comparison tools and full-text document search capabilities help to further streamline research. No other industry database matches PharmaCircle's breadth of content and multi-parameter search, filtering, and visualization capabilities. To learn more, email contact@pharmacircle.com, call (800) 439-5130, or visit **www.pharmacircle.com.**

Technology-Focused Biomanufacturing

RESILIENCE

Resilience is a technology-focused biomanufacturing company dedicated to broadening access to complex medicines (biologics, vaccines, nucleic acid, cell and gene therapy modalities and drug product). Founded in 2020, the company is building a sustainable network of high-tech, end-to-end manufacturing solutions to ensure the treatments of today and tomorrow can be made quickly, safely, and at scale. By continuously advancing the science of biopharmaceutical manufacturing and development, Resilience seeks to free its partners to focus on the discoveries that improve patients' lives and protect biopharmaceutical supply chains against future disruptions. For more information, visit Resilience at **www.resilience.com.**

Full-Service CDMO

VETTER

Vetter is a leading independent contract development and manufacturing organization (CDMO) that specializes in the clinical and commercial aseptic filling and packaging of syringes, cartridges, and vials. The company has extensive experience with biologics and other complex compounds. Collaborating with pharma/biotech clients worldwide, Vetter supports products from preclinical development through global market supply. Through its US and European facilities, Vetter Development Service provides state-of-the-art support for early-stage products, with transfer at Phase III to Vetter Commercial Manufacturing for large-scale production. For more information, visit Vetter at **www.vetter-pharma.com.**

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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 small molecule expertise focusing on oral dosage forms. Adare's specialized technology platforms provide taste masking, customized release, solubility enhancement, and patient-centric dosing solutions. With a proven history in drug delivery, Adare's seven facilities in the US and Europe have developed and manufactured more than 65 products sold by customers worldwide.

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