Drug Development® & Delivery

September 2024 Vol 24 No 6 www.drug-dev.com

Injection Devices: Becoming More Efficient

The Science & Business of Pharmaceutical and Biological Drug Development

IN THIS ISSUE

INTERVIEW WITH COYA THERAPEUTICS' FOUNDER & CEO **HOWARD BERMAN, PHD**

ARTIFICIAL INTELLIGENCE 16
Emilio Cordova

SOLUBILITY TECHNOLOGIES 24
Timothy Pas, PhD
Vincent Levet, PhD

CLINICAL TRIALS 70
Melissa Mooney

TECHNOLOGY & SERVICES SHOWCASES 72

Suzanne Saffie-Siebert, PhD
Next-Generation Delivery of RNA Therapeutics

Lu Tian, PhD
Viewing Lipid Nanoparticle Delivery Technology Through the Lens of a CRDMO

Cindy H. Dubin
From Pens & Autoinjectors to Pills, Sprays & Capsules, Injections Become More Efficient

abbvie | Contract Manufacturing

Vision. Expertise. Success.

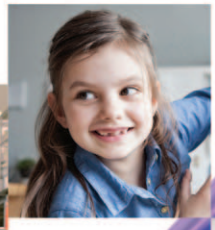
Eyecare | Topical | Aseptic Fill-Finish | Hot Melt Extrusion (HME) | Oral Solid Dose
Microbial Fermentation | Biologics | Antibody Drug Conjugate (ADC) | Custom API

AbbVie Contract Manufacturing partners with companies around the globe to develop, scale and manufacture their pharmaceutical products.

With decades of experience, we see the complete picture to deliver your vision and real-world results, while improving people's lives.

Start the journey, at abbviecontractmfg.com

Vision.
Expertise.
Success.



CMO LEADERSHIP AWARDS2022 CAPABILITIES
CMO LEADERSHIP AWARDS2022 SERVICE
CMO LEADERSHIP AWARDS2022 RELIABILITY
CMO LEADERSHIP AWARDS2022 QUALITY
CMO LEADERSHIP AWARDS2022 EXPERTISE
CMO LEADERSHIP AWARDS2022 COMPATIBILITY

CAPTISOL®

A LIGAND TECHNOLOGY

Oral use of Captisol* is here.

Applications and benefits include:

- Chronic use
- Pediatric dosing
- Preservative-sparing
- Increase bioavailability
- Mask unpleasant tastes

Our Team is Ready. Are you?
Contact us today!
858.550.5632 | cdinfo@captisol.com

Captisol.com

*Captisol is a sulfobutyl ether beta cyclodextrin

Drug Development & Delivery

September 2024 Vol 24 No 6

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

Aidaptus®

2-step single-use auto-injector platform

Versatile design

intuitive delivery

reddot winner 2023
innovative product

Your fill volume may change, with Aidaptus® **auto-adjust plunger technology** your auto-injector doesn't need to

Now in production

Accommodates both 1mL and 2.25mL glass syringes in the same device

See our auto-adjust plunger technology in action

Find out more by scanning the QR code or visiting **ompharmaservices.com/ddd-sept2024**

In collaboration with Stevanato Group

*In addition to an air bubble and overfill

OMPS/ddd/ad/ob/0924/7

Owen Mumford
Pharmaceutical Services

Injection Devices: Becoming More Efficient

"The pharma community has made incredible advancements in developing injectable devices that are less painful, ensure precise drug delivery, reduce injection frequency, and integrate with digital health technologies – all of which are important for patients treating chronic diseases. As the comfort level for patients to self-administer medication rises, so too does the global injection drug delivery market. Estimated to be valued at $757.06 billion this year, the market is projected to reach 1,630.73 billion by 2033, according to Nova One Advisor."

p.34

Departments

Market News & Trends.....10
Technology & Services Showcase.....72

Table of Contents

Artificial Intelligence

16 **Accelerating Drug Discovery & Development: The AI Revolution is Here**
Emilio Cordova delves into how AI is transforming the drug discovery sector by enhancing predictability and efficiency and explains her company's unique approach.

Formulation Development

24 **Solubility-Enhancing Technologies in Pharmaceutical Development, a Mini-Review**
Timothy Pas, PhD, and Vincent Levet, PhD, believe different solubility-enhancing technologies can be used by developers, and with different advantages and drawbacks, linked to payload, manufacturability, tolerability, and physical and chemical stability, effectively navigating solubility-enhancing solutions is multifaceted.

Special Feature

32 **Injection Devices: From Pens & Autoinjectors to Pills, Sprays & Capsules, Injections Become More Efficient**
Contributor Cindy H. Dubin reports on innovative and promising injection technologies that are ever more user friendly, versatile, precise, and life-saving.

Executive Interview

52 **Coya Therapeutics – Unlocking the Power of Tregs to Combat Inflammation & Fight Neurodegenerative Diseases**
Dr. Howard Berman, Founder and CEO of Coya Therapeutics, discusses how the company is leveraging Tregs, its investigational products and the conditions targeted, Coya's significant partnership with Dr. Reddy's Laboratories, and his goals throughout the next 5 years.

Drug Delivery

56 **Viewing Lipid Nanoparticle Delivery Technology Through the Lens of a CRDMO**
Lu Tian, PhD, says the complexity of LNP formulations demands diverse and integrated capabilities for development – incorporating lipids, oligonucleotides, small molecules, and sometimes antibodies or ligands, and thus it requires a cohesive approach.

Silicon-Stabilized Hybrid LNPs

61 **Next-Generation Delivery of RNA Therapeutics**
Suzanne Saffie-Siebert, PhD, Michael Welsh, PhD, Nissim Torabi-Pour, PhD, and Flavia M. Sutera, PhD, review current shortcomings, as well as some accompanying manufacturing challenges, and will show how they can be addressed by SiSaf's silicon-stabilized hybrid LNPs.

Clinical Trials

70 **Faithful Migration: Shifting Patient Reported Outcomes From Paper to Electronic**
Melissa Mooney says by following certain steps to faithful migration, the shift to electronic measures is efficient and reliable, especially as there is an increasing body of evidence showing that when minor changes are made to an original measure, the resulting ePRO is likely to be considered equivalent.

ASCENDIA PHARMA

Start your project within weeks; not months.

From pre-formulation to Phase III and commercial supply, Ascendia is the CDMO Partner of Choice for your most challenging projects.

Ascendia Pharma's combination of proprietary nanotechnologies and their BEST culture philosophy makes us a Partner of Choice for people with projects from complex formulations to commercial supply needs.

Technical Services from Ascendia:

- Rapid Early-stage Development Services
- Poorly Soluble & Low Bioavailability Drug Formulations
- LNP's for Vaccines, mRNA & Gene Therapy.
- cGMP Sterile & Non-sterile Clinical Trial Materials
- Sophisticated Formulations (Biologics & Small Molecules)
- 505(b)(2) Product Development

Contact Ascendia to find out how we can ***Make the Impossible Possible*** for you!

ASCENDIA PHARMA

732-658-4267

bd@ascendiapharma.com

www.ascendiapharma.com

Sonoma Biotherapeutics Receives $45-Million Milestone Payment From Regeneron

Sonoma Biotherapeutics, Inc. recently announced it has received a $45-million milestone payment from Regeneron Pharmaceuticals, Inc., under the terms of its active collaboration to discover, develop and commercialize engineered Treg therapies for autoimmune diseases.

"This payment marks a significant milestone in our evolution as a company and our collaboration with Regeneron, which has been going extremely well," said Jeff Bluestone, PhD, Chief Executive Officer of Sonoma Bio. "The cutting-edge Regeneron technology for target identification and animal models, combined with Sonoma Bio's Treg and cell therapy expertise, has enabled an effective collaboration in developing new treatment options for patients suffering from devastating autoimmune diseases."

In March 2023, Sonoma Bio entered into a collaboration and license agreement with Regeneron to research, develop and commercialize Treg cell therapies for inflammatory bowel disease and two other undisclosed indications, with a Regeneron option for a fifth indication. The collaboration integrates Regeneron's industry-leading VelociSuite technologies for the discovery and characterization of fully human antibodies and T cell receptors (TCRs) with Sonoma Bio's pioneering approach to developing and manufacturing gene-modified Treg cell therapies.

Under the terms of the agreement, Sonoma Bio received $75 million in upfront payments, which included a $30 million equity investment in Sonoma Bio by Regeneron. Sonoma Bio was also eligible to receive an additional $45 million development milestone payment, which has now been achieved. The parties are equally co-funding research and development for all potential products and will share equally any future commercial expenses and profits. Regeneron will have the option to lead late-stage development and commercialization on all products globally, with Sonoma retaining rights to co-promote all such products in the US.

Sonoma Bio continues to retain full ownership of its lead Treg cell therapy candidate, SBT-77-7101, and other programs in development. The company has two ongoing Phase 1 trials of SBT-77-7101 in rheumatoid arthritis and hidradenitis suppurativa.

Sonoma Biotherapeutics is a clinical-stage biotechnology company developing engineered regulatory T cell (Treg) therapies to treat serious autoimmune and inflammatory diseases by restoring balance to the immune system. Founded by pioneers in Treg biology and cell therapy, the company is employing proprietary platform technologies and approaches to develop a new generation of targeted and durable Treg cell therapies. Sonoma Biotherapeutics is based in South San Francisco and Seattle. For more information, visit sonomabio.com.

Recipharm Introduces ReciPredict to Revolutionize Drug Product Development & Manufacturing

Recipharm recently announced the launch of ReciPredict, a cutting-edge platform for Quality by Design (QbD), designed to transform the landscape of drug product development, tech transfer and manufacturing. With its innovative combination and systematic application of material sciences, statistical tools and modelling and simulation, ReciPredict promises to deliver unparalleled efficiency and reliability to the pharmaceutical industry, by streamlining the product development cycle, from initial formulation through to manufacturing.

Dr. Uwe Hanenberg, PhD, Head of Product Implementation, said "ReciPredict accelerates the journey of new drugs to the clinical stage by 3-6 months, substantially expediting the drug development process. It also offers significant cost savings by reducing API consumption by 30% to 70%. Another crucial advantage is that applying ReciPredict de-risks tech transfers by identifying the right parameters for best process robustness, consequently achieving consistent and high-quality results. This is a win-win for our customers and for patients, as it helps bring new drugs to market faster."

ReciPredict combines expertise in data science and statistics with powerful modelling and statistical tools. By leveraging advanced statistical models, ReciPredict connects critical process parameters, material attributes and drug product quality attributes. This comprehensive understanding enables Quality by Design with precise prediction of quality attributes based on material properties and process parameters.

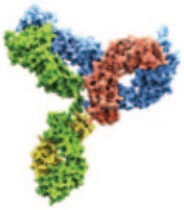
Uwe Hanenberg continues "ReciPredict offers an unparalleled understanding of materials and processes, enabling faster and more efficient drug development. As such, it provides great efficiencies by solving complex problems in product development, tech transfers, and routine manufacturing. Our key capabilities include an expert data science and statistics team, advanced modelling tools, comprehensive statistical tools, powder characterisation (FT4, Accupyc, BET, and more), and a Style One Evo compression and compaction simulator. These features collectively ensure that ReciPredict stands out as a robust and reliable platform in the pharmaceutical industry."

ReciPredict can be utilized across various stages and aspects of drug development and manufacturing, including: product development, trial design and DoE, data analysis, In Silico formulations, tech transfers and process & formulation optimisation. ReciPredict is versatile and can be applied to all sites, products and technologies, making it an invaluable tool for any pharmaceutical company looking to enhance their drug development and manufacturing processes.

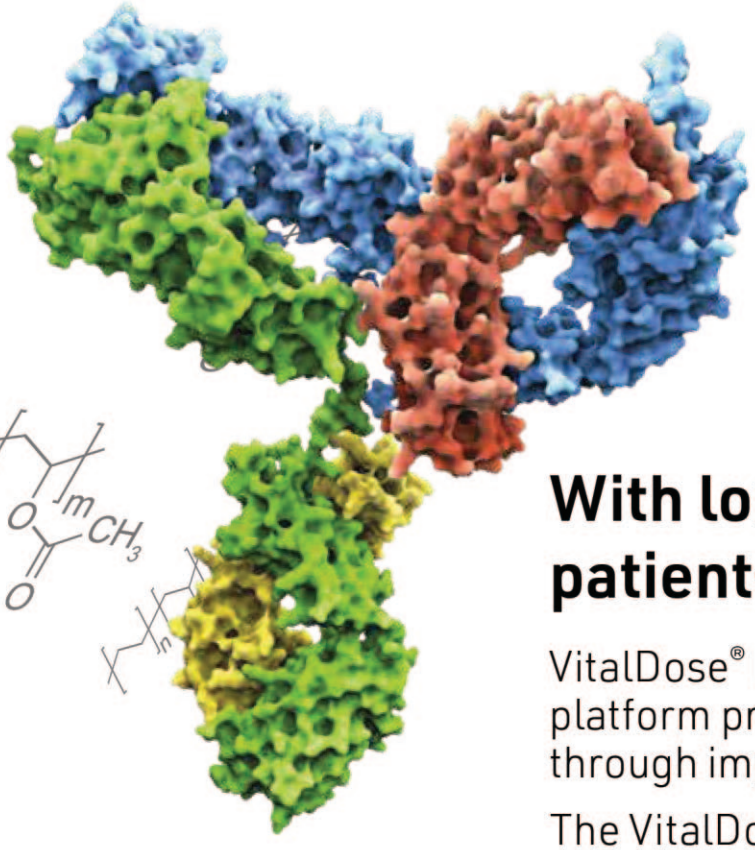
Recipharm is a leading Contract Development and Manufacturing Organisation (CDMO) employing over 5,200 employees worldwide. Recipharm provides manufacturing services of pharmaceuticals in various dosage forms, including sterile fill & finish, oral solid dosage and biologics; clinical trial material development and manufacturing services; and pharmaceutical product development. Its biologics segment, ReciBioPharm, works with customers to develop and commercialise advanced therapy medicinal products (ATMPs): pre-clinical to clinical development, commercial development and manufacture for new biological modalities, encompassing technologies based on live viruses and viral vectors, live-microbial biopharmaceutical products, nucleic acid-based mRNA and plasmid DNA production.

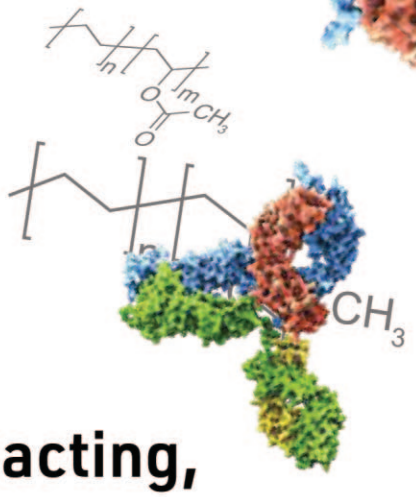
Celanese

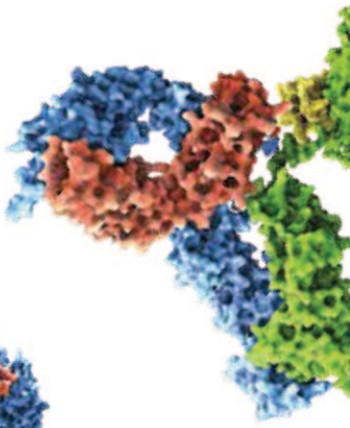
VITAL Dose®



Sustained Drug Delivery







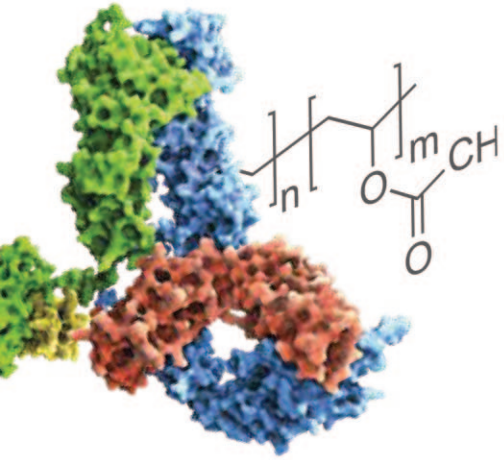
With long-acting, patient-centric therapeutics

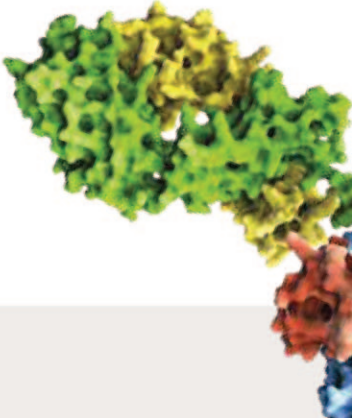
VitalDose® EVA is a copolymer drug-delivery platform providing controlled release through implant and insert dosage forms.

The VitalDose® platform is flexible and customizable with high drug loading capacity (≤75%).

Our scientists and engineers will partner with you to create novel delivery systems for:

- mAbs
- Small molecules
- Peptides
- RNA





Collaborate with us

Email: Healthcare@Celanese.com

Website: Vitaldose.com

Kymanox & SHL Medical Enter Non-Exclusive Strategic Partnership Agreement to Support Delivery of Modern Medicines

Kymanox Corporation and SHL Medical AG recently announced they have signed a non-exclusive strategic partnership agreement. This collaboration establishes a reciprocal preferred partnership between the two industry leaders, combining Kymanox's extensive professional services offering and combination products expertise and SHL's innovative drug delivery solutions, including autoinjectors, pen injectors, and specialty delivery systems for large-volume and high-viscosity formulations.

Recognizing the importance of early engagement, the partnership aims to streamline communication and cooperation between the parties, ultimately adding significant value and efficiency to the drug delivery, development, and commercialization process. The partnership will allow SHL to recommend Kymanox as a trusted professional services firm, renowned for its comprehensive and holistic services spanning early development to commercialization and beyond. Kymanox customers choosing SHL as their device partner will enjoy the collective benefits of this collaboration, including access to shared resources, expertise, and the collective commitment of both companies to deliver high-quality, patient-centric solutions, with each of the organizations focusing on their respective strengths.

"SHL recognizes the importance of fostering relationships between leading players in the drug delivery industry, as no single company can address the complexities of the pharmaceutical landscape alone," said Markus Puusepp, Chief Growth Officer at SHL Medical. "We are excited to solidify our strategic partnership with Kymanox, as their unparalleled experience in supporting product commercialization complements SHL's commitment to providing cutting-edge drug delivery solutions. Our collaboration is a testament to the shared vision of bringing high-quality device solutions to the market efficiently."

The non-exclusive partnership allows Kymanox to continue forging relationships with device manufacturers, pharmaceutical and biotech companies, contract development and manufacturing organizations (CDMOs), and fill-finish providers in the industry. This collaboration is part of Kymanox's vision of creating a dynamic network of leading life sciences organizations as "Kymanox Preferred Partners", promoting shared learning and continuous improvement, and building a comprehensive support system across all stages of drug development and the product lifecycle. For SHL Medical, the partnership enhances its Alliance Management Program, further bolstering the company's vertically integrated business model by facilitating customer engagement with other key players within the drug delivery ecosystem and providing customers seamless access to a full network of solutions and services. Through this strategic alliance, both companies aim to enhance their respective offerings and drive innovation in the life sciences industry.

Matt Neighoff, Chief Commercial Officer at Kymanox, stated "Kymanox is proud to continue its strategic collaborations within the healthcare industry, exemplified by the strengthened partnership with SHL, a leader in the design, development, and manufacturing of advanced drug delivery solutions. This agreement demonstrates the companies' joint commitment to supporting our customers on their journey to deliver innovative medicines to patients. We have seen how similar strategic partnerships have helped streamline development projects for our clients and reduced cost and risk. Together, we aim to empower pharmaceutical and biotech companies, ensuring high-quality products reach patients swiftly and efficiently because patients deserve better."

Allyx Therapeutics Announces First Parkinson's Disease Patient Treated

Allyx Therapeutics recently announced the first patient has been dosed with its lead compound, ALX-001, in a new clinical study assessing safety, pharmacokinetics and potential therapeutic response in patients with Parkinson's disease. ALX-001 is a highly selective, first-in-class, synapse-targeted, disease-modifying oral therapy. Allyx Therapeutics is a clinical-stage biotechnology company working to deliver a novel approach to preserve and protect synapses for people living with neurodegenerative diseases.

"Allyx Therapeutics is moving forward with strong momentum to develop ALX-001 as the first-ever disease-modifying small molecule for neurodegenerative diseases, with two concurrent safety studies in patients with Parkinson's disease and with Alzheimer's disease, adding important information to the body of knowledge for this novel therapeutic approach," said Tim Siegert, PhD, Chief Operating Officer and co-founder of Allyx Therapeutics.

The 28-day Parkinson's disease study (NCT06309147) is assessing the safety of ALX-001 dosed twice daily at either 50 mg or 100 mg versus placebo in adults between 21 and 80 years of age, and will also investigate dopamine transporter levels in the brain measured with single photon emission computed tomography as an early marker of therapeutic response to a treatment that targets synapse restoration. The study is being conducted by the Duke Clinical Research Institute (DCRI) and is supported with grant funding awarded to Allyx Therapeutics from The Michael J. Fox Foundation for Parkinson's Research.

"I'm excited to collaborate with the Allyx team as we advance understanding of how Parkinson's disease affects the brain and what more we might be able to do to provide a real impact for patients. Investigating the safety of this disease-modifying small molecule is a crucial first step, and one I'm proud to be a part of," said Laurie H. Sanders, PhD, Associate Professor of Neurology at Duke University School of Medicine and DCRI.

Building on twelve years of clinical research, ALX-001 continues to demonstrate promise in ongoing studies. The ALX-001 program has received more than $20 million in grant funding from the National Institutes of Health, the US Government's highly competitive Small Business Innovation Research (SBIR) programs, the Alzheimer's Association, and The Michael J. Fox Foundation for Parkinson's Research, among others.

ALX-001 (previously BMS-984923) is a silent allosteric modulator of mGluR5, and is a first-in-class compound that selectively blocks the pathogenic activation of the receptor while preserving the normal physiological glutamate signaling that is required for cognition. As such, ALX-001 has a wide therapeutic window that can saturate receptors while avoiding on-target toxicity observed with negative allosteric modulators. mGluR5 has been shown to be essential for mediating synaptic dysfunction and loss caused by multiple misfolded extracellular protein species, and as such, presents a novel approach for treating Alzheimer's and Parkinson's disease. Importantly, ALX-001 is an orally bioavailable and brain penetrant small molecule with demonstrated mGluR5 selective engagement. The molecule was originally identified by Bristol Myers Squibb, but the mechanism of action for neurodegenerative diseases and the identification of ALX-001 as disease-modifying for Alzheimer's disease was discovered by Allyx scientific founder Stephen Strittmatter at Yale School of Medicine. Allyx Therapeutics obtained an exclusive worldwide license for ALX-001 from Bristol Myers Squibb and Yale School of Medicine.

Novartis Begins Construction of Two New Radioligand Therapy Facilities in the US

Novartis recently announced the construction of two new radioligand therapy (RLT) manufacturing facilities in the US that will extend its world-class manufacturing and supply chain capabilities. The new facilities represent Novartis' continued investment in developing a robust infrastructure to support the expanding use of RLTs to treat cancer.

Novartis broke ground on a new facility at its Indianapolis site that will produce radioisotopes critical for the manufacturing of RLTs. In Carlsbad, CA, Novartis is establishing its third RLT manufacturing site in the US to support expanded use of RLTs, create resiliency in its manufacturing network and optimize the delivery of medicines to patients on the West Coast.

RLTs are a form of precision medicine that combine a tumor-targeting molecule (ligand) with a therapeutic radioisotope, enabling the delivery of radiation to the tumor while limiting damage to the surrounding cells. Novartis is actively investigating the application of RLTs across cancer types and settings, with one of the deepest and most advanced pipelines in the industry. Both facilities will be built with room for further expansion to enable the potential production of different isotopes, ligands and RLTs. Once completed and approved, these new facilities will further strengthen the Novartis RLT manufacturing and supply network.

"Novartis pioneered the adoption at scale of radioligand therapies across different indications as a targeted approach to treat cancers," said Victor Bultó, President, US, Novartis. "Building on this experience and knowledge, we are confident in the potential of RLTs to meaningfully benefit many more patients affected by different types of cancer in the future. We are investing in our supply chain capabilities today to ensure that we are prepared to consistently deliver these complex treatments to the growing number of eligible patients in the long-term."

Novartis was the first to scale the availability of RLTs in the market across different cancer types with Pluvicto (lutetium Lu 177 vipivotide tetraxetan) and Lutathera (lutetium Lu 177 dotatate). The company's early and late-stage pipeline has several programs in or entering the clinic, as well as other preclinical and discovery programs to identify the next wave of RLTs. Following regulatory approvals, isotopes produced in Indianapolis will be used to manufacture Pluvicto, Lutathera, and investigational RLTs in Novartis' pipeline.

Longeveron Announces Positive Type C Meeting With FDA Regarding Pathway to BLA

Longeveron Inc. recently announced the positive Type C meeting with the US FDA supporting the advancement of Lomecel-B, a proprietary, scalable, allogeneic, investigational cellular therapy currently being evaluated in a Phase 2b clinical trial (ELPIS II) for hypoplastic left heart syndrome (HLHS).

The company and the FDA reached foundational alignment on the primary endpoint and secondary endpoints for ELPIS II. The FDA confirmed that, with several conditional requirements to be accomplished, ELPIS II may be deemed pivotal, and, if positive, acceptable for Biological License Application (BLA) submission for full traditional approval. Among other items, the Company will need to submit its prespecified Statistical Analysis Plan (SAP) and Chemistry, Manufacturing and Controls (CMC) readiness plan, including Lomecel-B stability and comparability data, to the FDA for prior review.

"We are pleased to have alignment with FDA on the development pathway for our Lomecel-B development program in HLHS, which has a devastating impact on patients and their families," said Wa'el Hashad, Chief Executive Officer of Longeveron. "While we have a lot of work yet to do, the potential for ELPIS II to serve as the foundation for a BLA submission significantly reduces the time to reach submission and potential approval of Lomecel-B as an HLHS adjunct therapy."

ELPIS II builds on the positive clinical results of ELPIS I, in which children in the trial experienced 100% transplant-free survival up to five years of age after receiving Lomecel-B compared to an approximate 20% mortality rate observed from historical control data.

ELPIS II is being conducted in collaboration with the National Heart, Lung, and Blood Institute (NHLBI) through grants from the National Institutes of Health (NIH).

The Lomecel-B HLHS program has received three FDA designations: Orphan Drug designation, Fast Track designation and Rare Pediatric Disease designation. Under the Rare Pediatric Disease designation, if Longeveron were to receive FDA marketing approval for Lomecel-B for HLHS, the company could be eligible to receive a Priority Review Voucher.

Lomecel-B is an allogeneic, investigational product made from specialized cells isolated from the bone marrow of young healthy adult donors. These specialized cells, known as medicinal signaling cells (MSCs), are essential to the endogenous biological repair mechanism. MSCs have shown high promise for cardiac regenerative therapy (Kaushal and Wehman 2015; Wehman et al. 2016). They also have been shown to respond to sites of injury or disease and secrete bioactive factors that are anti-inflammatory and regenerative. Longeveron believes that Lomecel-B may have multiple potential mechanisms of action that may lead to anti-inflammatory, pro-vascular regenerative responses, and therefore may have broad application for a range of rare and aging related diseases.

Nuvectis Pharma Announces Orphan Drug Designation for the Treatment of ARID1a-Deficient Ovarian, Fallopian Tube & Primary Peritoneal Cancers

Nuvectis Pharma, Inc. recently announced that NXP800 was granted Orphan Drug Designation by the US FDA for the treatment of AT-rich interactive domain-containing protein 1a (ARID1a) ARID1a-deficient ovarian, fallopian tube, and primary peritoneal cancers.

Ron Bentsur, Chairman and Chief Executive Officer of Nuvectis, said "We are very pleased to have received this designation from the FDA for NXP800. The prevalence of ovarian cancer, which is comprised of ovarian, fallopian tube and primary peritoneal cancers, exceeds the 200,000 patient threshold below which drugs may be eligible to receive Orphan Drug Designation in the US and in ovarian cancer it has been uncommon to receive this designation for the treatment of a subset of the disease. We therefore believe that this Orphan Drug Designation granted by the FDA for NXP800 for the treatment of a subset of ovarian cancer, specifically for patients with an ARID1a deficiency, provides further validation for NXP800's mechanism of action and the target patient population in our ongoing Phase 1b clinical trial in patients with platinum resistant, ARID1a-mutated ovarian cancer. We expect to provide a data update from this study this coming fall."

Orphan Drug Designation is granted by the FDA to drugs or biologics intended to treat a rare disease or condition, defined as one that affects fewer than 200,000 people in the US. Orphan Drug Designation provides certain financial incentives to support clinical development, and the potential for up to seven years of marketing exclusivity for the product for the designated orphan indication in the US if the product is approved for its designated indication.

Nuvectis Pharma, Inc. is a biopharmaceutical company focused on the development of innovative precision medicines for the treatment of serious conditions of unmet medical need in oncology. The company is currently developing two clinical-stage drug candidates, NXP800 and NXP900. NXP800 is an oral small molecule GCN2 activator currently in a Phase 1b clinical trial for the treatment for platinum resistant, ARID1a-mutated ovarian carcinoma and in an Investigator-sponsored clinical trial for the treatment of cholangiocarcinoma. The US FDA granted Fast Track Designation to the NXP800 development program in platinum resistant, ARID1a-mutated ovarian carcinoma, and Orphan Drug Designation for the treatment of cholangiocarcinoma and ARID1a-deficient ovarian, fallopian tube, and primary peritoneal cancers. NXP900 is an oral small molecule inhibitor of the SRC Family of Kinases (SFK), including SRC and YES1. NXP900 has a unique mechanism of action in that it inhibits both the catalytic and scaffolding functions of the SRC kinase thereby providing complete shutdown of the signaling pathway. NXP900 is currently in a Phase 1a dose escalation study.

Ocean Biomedical Announces Patent Issued for PfGARP Malaria Antibodies

Ocean Biomedical recently announced its Scientific Co-founder Dr. Jonathan Kurtis, MD, PhD, has been issued a key US patent for his groundbreaking malaria therapeutic antibody discovery that targets PfGARP. Since publicizing news of his original research on PfGARP and its critical role in the malaria cycle in the Journal NATURE, Dr. Kurtis and his team have been working to deepen their understanding of how it naturally triggers the death of malaria parasites, and their control of that mechanism. Their expanded insights have already led to: 1.) a powerful vaccine candidate targeted for long term prevention of malaria infection; 2.) a therapeutic antibody candidate for short-term malaria prevention; and 3.) a therapeutic small molecule drug candidate targeted to treat severe malaria, with potential to launch a whole new class of malaria medicines.

This patent is adding to Ocean Biomedical's global patent portfolio of over 5 dozen patents for discoveries with potential to impact major unmet medical needs in infectious disease, oncology, and fibrosis, developed through grants totaling over $125M.

Kurtis' novel approach causes parasite death at a key stage in the malarial cycle, triggering programmed cell death through apoptosis. This patent expands protection for Dr. Kurtis' novel discoveries at a time when the most common strains of malaria are showing signs of growing resistance to current Artemisinin-based drugs.

"Inducing parasite cell death via targeting PfGARP is a novel approach that has potential to result in a whole new class of antimalarial interventions, including mRNA-based vaccines, small molecule drugs and our current monoclonal antibody," said Dr. Kurtis. "Our monoclonal antibody and small molecule drug comes at a critical time because malaria parasites are developing resistance to current frontline therapeutics, and the currently approved vaccine offers only very limited protection."

Malaria is the greatest single-agent killer of children on the planet, killing approximately 627,000 individuals in 2022. Artemisinin-based drug therapy remains the mainstay of treatment, but the spread of parasites resistant to this family of compounds threatens recent progress achieved by antimalarial campaigns and underscores the urgent need to identify new antimalarial drugs.

"At each step in the process we are learning more about how this 'kill switch' mechanism works to interrupt the malaria parasite's lifecycle, and how we can exploit that on the prevention side and the treatment side," said Dr. Jake Kurtis, Scientific Co-founder of Ocean Biomedical, member of Ocean Biomedical's board of directors and Chair of Pathology and Laboratory Medicine at the Warren Alpert Medical School Brown University.

"The progress we have been able to make thus far in advancing novel targets is a testament to Ocean Biomedical's innovative model and deep partnership with premier research institutions. We are hopeful that Dr. Kurtis' discoveries will lead to powerful new treatment options that can save hundreds of thousands of lives, and we are proud to be leading in this important work," added Elizabeth Ng, Chief Executive Officer of Ocean Biomedical.

Abata Therapeutics Receives FDA Fast Track Designation for Progressive Multiple Sclerosis Treatment

Abata Therapeutics recently announced the US FDA has granted Fast Track designation for ABA-101 for the treatment of patients with progressive multiple sclerosis (MS). The FDA recently cleared ABA-101's Investigational New Drug (IND) application, and initiation of a first-in-human (FIH) Phase 1 study is imminent.

"There are no effective treatments for progressive MS, and rapidly advancing new therapies is critical for patients and their families. We are very pleased that the FDA granted us Fast Track designation as it will enable us to expedite our efforts to bring ABA-101 to patients," said Samantha Singer, MS, MBA, President and Chief Executive Officer of Abata. "We are focused on initiating our Phase 1 study this year in patients and evaluating the potential impact of this important new therapy."

The FDA grants Fast Track designation to facilitate the development and expedite the review of drugs to treat serious conditions and fill an unmet medical need, with the ultimate goal of getting important new drugs to patients earlier. A drug that receives Fast Track designation may be eligible for more frequent meetings and communications with the FDA and rolling review of any application for marketing approval, which may lead to earlier drug approval and access for patients. A drug receiving Fast Track designation also may be eligible for Accelerated Approval and Priority Review if relevant criteria are met.

ABA-101 is Abata's autologous Treg therapy in development for the treatment of progressive multiple sclerosis. It was specifically designed for MS patients with progressive disease who have imaging evidence of ongoing inflammatory tissue injury and are HLA-DRB1*15:01 positive – an estimated patient group of about 45,000 in the U.S. today. ABA-101 is created by engineering a patient's own Tregs to express a T cell receptor (TCR) that specifically recognizes immunogenic myelin fragments in the CNS. This approach was designed to offer a strong safety profile and a highly localized anti-inflammatory effect at the site of disease. In in vivo preclinical studies, ABA-101 was well-tolerated and demonstrated antigen-dependent Treg functionality, anti-inflammatory cytokine production, suppression of the production of inflammatory cytokines and therapeutic effect.

Abata Therapeutics is dedicated to transforming lives with Treg therapies for severe autoimmune and inflammatory diseases. Founded by pioneers in Treg biology, TCR and antigen discovery, disease pathogenesis, and molecular and imaging biomarkers, Abata has developed a differentiated product engine to create engineered Treg cell therapies that are tissue-specific, robust, and durable. Abata's lead program in progressive MS is on track to initiate a Phase 1 study in 2024, and its second program in type 1 diabetes is in IND-enabling studies. Both indications are tissue-specific autoimmune diseases with substantial unmet need, supporting a strong rationale for Abata's Treg approach. The company was launched in 2021 by Third Rock Ventures, and today is supported by a diverse syndicate of investors, including Lightspeed Venture Partners, Biogen, Bristol Myers Squibb, ElevateBio, Eurofarma, Invus, Samsara BioCapital, and T1D Fund (formerly JDRF T1D Fund). Abata is based in Watertown, MA.

Emergex Receives Patent Protection for First-in-Class Influenza A Vaccines With Potential to Provide Long-Term T Cell Immunity

Emergex Vaccines Holding Limited recently announced it has received patent protection from the United States Patent and Trademark Office (USPTO) for its novel class of influenza vaccines that have the potential to provide long-term T cell immunity against all legacy strains of influenza A since 1918, as well as seasonal variants and heterosubtypic changes. This groundbreaking patent covers Emergex's vaccine comprising in part immunogenic peptides encoded by a negative sense open reading frame (ORF) from segment 8 of the influenza A genome. To Emergex's knowledge, this represents the first known patent for viral peptides derived from antigenomic translation suggesting that segment 8 of influenza A is ambisense (negative and positive sense ORFs). In addition, this grants the company exclusive rights to develop a vaccine that incorporates these immune elements, offering a level of immune recognition that existing flu vaccines are unable to provide either because of composition or method of administration. This also further expands Emergex's impressive portfolio of approximately 100 technology inventions across various technologies and jurisdictions.

A large ORF in the negative sense strand of segment 8 in human influenza A virus (NEG8) has been conserved for over 100 years. The length of the NEG8 ORF is represented by three epochs and each epoch change (ie, pandemic index strain) has corresponded to the onset of a global H1N1 pandemic. Although previously not thought to be translated, Emergex has successfully identified a number of peptides that are presented by MHC class I molecules on influenza-infected cells and that are encoded by NEG8. Cluster stacks of these NEG8-derived epitopes as determined by immunoproteomics are conserved across influenza A serotypes (epoch related) and are potential key targets for inducing heterologous CD8 T cell immunity and therefore are optimal for inclusion in pandemic preparedness vaccines. Additionally, incorporation of avian- and equine species-specific NEG8 derived peptides in a vaccine also has the potential to expand protection to zoonotic transmissions.

Professor Thomas Rademacher, Co-Founder and Chief Executive Officer at Emergex, said "Our research into NEG8 has revealed exciting potential for a new approach to influenza vaccines. We believe that a vaccine composition including conserved NEG8-derived MHC class I peptides could provide protection against past, existing, and emerging human influenza viruses, as well as prevent zoonotic influenza viruses from establishing themselves in the human population and causing a pandemic. Emergex aims to leverage this NEG8 epitope-containing vaccine to generate a durable and broadly-protective cellular immune response upon vaccination."

Emergex is set to advance its first-in-class influenza vaccine into the clinic, with Phase 1 trials anticipated to begin in the first half of 2025.

Emergex is a clinical-stage, privately held biotechnology company, headquartered in Abingdon, Oxon, UK, with an operating subsidiary in Doylestown, PA, a microneedle manufacturing facility in Fremont, CA, and GMP production vaccine facility in Milton Park, UK.

ARTIFICIAL INTELLIGENCE

Accelerating Drug Discovery & Development: The AI Revolution Is Here

By: Emilio Cordova

THE PARADIGMS, THEY ARE A-CHANGIN'

In the realm of drug discovery and development, the integration of artificial intelligence (AI) is not just a trend; it's a paradigm shift. Traditional methods, characterized by lengthy time lines, high costs, and significant failure rates, have long been a source of frustration and unsuccessful attempts at delivering new drug products to market.[1] But that is set to change … profoundly.

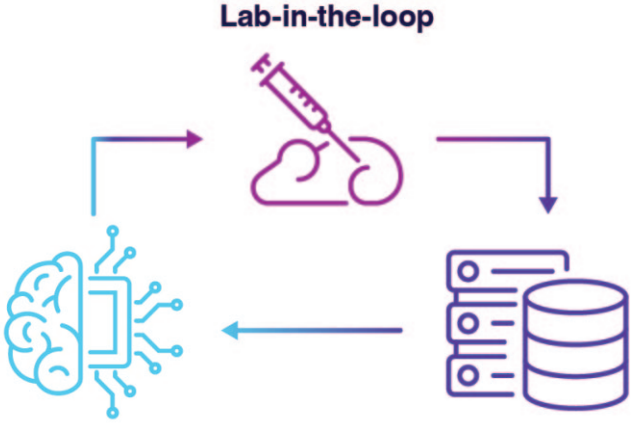
Enter AI, which offers more than just a beacon of hope; its skillful integration with existing drug discovery and development methods and human expertise promises more certainty in less time — with lower costs — benefiting sponsors, patients, and all other stakeholders.[2] The following delves into how AI is transforming the drug discovery sector by enhancing predictability and efficiency. It will also explain our unique approach, and why Logica® stands at the forefront of this ongoing revolution, democratizing access to cutting-edge drug discovery tools for companies of all sizes.

THE AI-DRIVEN TRANSFORMATION IN DRUG DISCOVERY

The journey of drug discovery has always been fraught with challenges. However, the advent of AI is rewriting the narrative. By embedding AI into the drug discovery process, we're witnessing a significant enhancement in every phase of discovery, from target identification to lead optimization and more. This integration is not merely about accelerating the process, but about improving it by instilling a level of predictability and efficiency that were previously unattainable using traditional methods.

THE POWER OF DATA IN REALIZING AI'S POTENTIAL

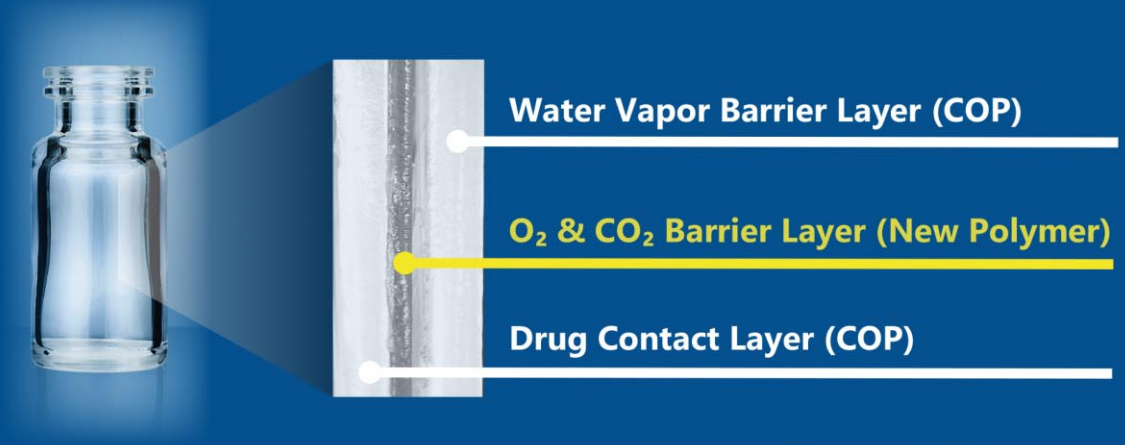
At the heart of AI's success in drug discovery is the quality of the data ingested.[3] AI thrives on data — preferably, lots of it — and its integration into the drug discovery process creates a powerful feedback loop. This loop, enriched by deep experimental expertise — again, more is better — not only refines AI models, but also ensures they evolve in tandem with emerging scientific insights, thereby enhancing their predictive accuracy and operational effectiveness. Consequently, this symbiosis between AI and data transcends traditional discovery methods, paving the way for a new era of innovation where breakthroughs are faster and more aligned with human biology.



OXYCAPT™ Multilayer Plastic Vial

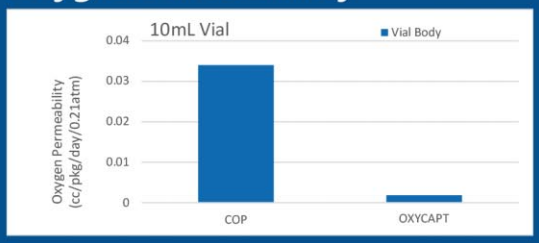
for Biologics & Cell Gene Therapy Products

Multilayer Structure

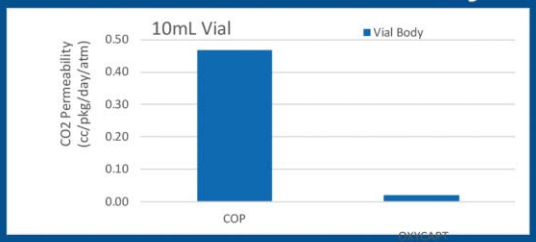


- Excellent O_2 & CO_2 Barrier
- Excellent UV Barrier
- Very Low Extractables
- Very Low Protein Adsorption
- High Compatibility with High & Low pH Drugs
- Excellent Break Resistance at Deep Cold Temp.
- Excellent CCI at Deep Cold Temp. with Dry Ice
- Maintain Excellent CCI after Freezing & Thawing Process

Oxygen Permeability

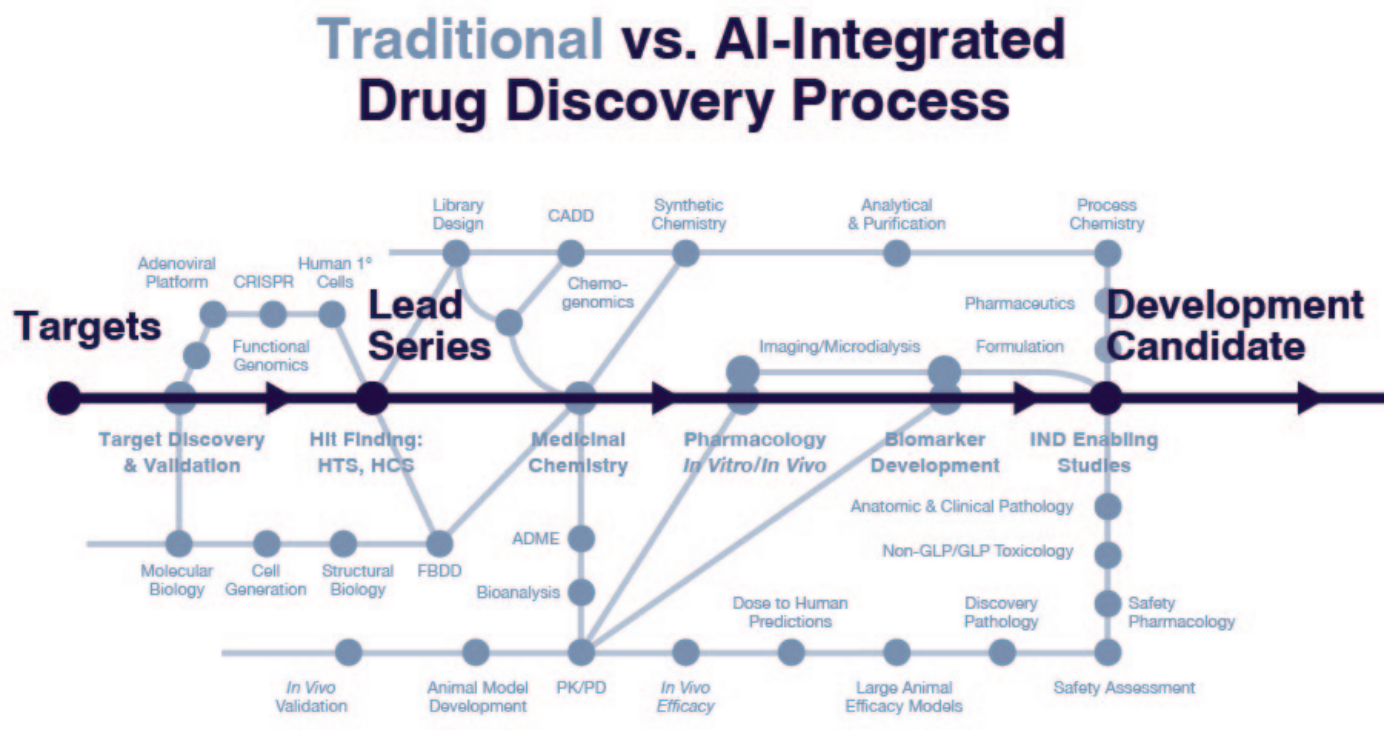


Carbon Dioxide Permeability



MITSUBISHI GAS CHEMICAL

Mitsubishi Gas Chemical Company, Inc.
https://www.mgc.co.jp/eng/products/abd/oxycapt.html
Mitsubishi Gas Chemical America, Inc.
http://www.mgc-a.com
Mitsubishi Gas Chemical Europe GmbH
https://www.mgc-europe.de



THE ROLE OF EXPERIMENTAL DATA IN AI-DRIVEN DISCOVERY

The synergy between AI and experimental data is pivotal. The "wet science" data serve as the foundation for training AI models, optimizing outputs, and improving program success. This symbiotic relationship ensures that AI models are not operating in a vacuum but are continually refined by real-world experimental results, leading to more accurate predictions and optimized strategies.[4]

THE FOUNDATION OF AI MODELS

Experimental data are the lifeblood of AI in drug discovery, encompassing a wide range of information — from biochemical interactions and phenotypic responses to pharmacokinetics and toxicology profiles. These data do more than just feed AI models; they shape their architecture, guiding the learning process to reflect biological realities. By training AI models with diverse and comprehensive datasets, we ensure that the insights and predictions they generate are grounded in the complex nuances of human biology.

OPTIMIZING OUTPUTS THROUGH CONTINUOUS LEARNING

One of the most compelling aspects of AI in drug discovery is its ability to learn and improve over time. Each new experiment contributes data that can be used to refine the model's predictions, making them increasingly accurate. This iterative process is akin to an ongoing dialogue between the laboratory bench and computational algorithms, where each cycle of feedback sharpens AI's focus and enhances its predictive power. For instance, data from a failed compound can reveal as much about target pathways as a successful one, teaching the AI to navigate the chemical space with greater discernment.

IMPROVING PROGRAM SUCCESS WITH DATA-DRIVEN DECISIONS

The ultimate goal of marrying AI with experimental data is to elevate the success rates of drug discovery programs, a long-standing sore spot in this industry. By leveraging AI's analytical prowess, researchers can *identify the most promising compounds early in the discovery process,* prioritize them for development, and anticipate potential challenges in safety and efficacy. This approach not only accelerates the pace of discovery, but also allows resources to be allocated more effectively, focusing the attention of sponsors on candidates with the highest likelihood of clinical success.

Ophthalmic plus
Simplify the application of eye drops

CPHI Worldwide | October 8–10, 2024 | Milano, Italy | Hall 20, Booth 20B1

Unique bottom design

Designed to be pressed on the bottom of the bottle

- 60% less finger force to create a drop
- Excellent choice for users with limited mobility in hands
- Ergonomic arm and wrist position

GERMAN PACKAGING AWARD
FUNCTIONALITY & CONVENIENCE
WINNER 2024

In cooperation with
PACKSYS INNOVATIONS

gerresheimer.com

gerresheimer
innovating for a better life

REAL-WORLD APPLICATIONS

Logica's approach exemplifies the power of this synergy. By integrating vast datasets from Charles River's experimental platforms with Valo Health's AI capabilities, Logica is equipped to develop models that accurately predict the outcomes of drug discovery endeavors. For example, AI can be used to model the pharmacodynamics of a new oncology drug, using data from early stage experiments. The model's predictions can then be used by team members to adjust the compound's structure, enhancing its efficacy, and reducing off-target effects, thereby streamlining the path to preclinical trials. This iterative, data-driven process is built to accelerate development cycles and increase the likelihood of clinical success — the collective goal of our industry. This approach represents a paradigm shift in how we understand and apply the principles of pharmacology and drug design, marking a new era of precision and efficiency in the quest to bring potentially lifesaving treatments to market.

ENGINEERING THE FUTURE: AI-DESIGNED MOLECULES & BEYOND

The future of drug discovery is being reshaped by the convergence of AI and experimental data, a partnership that promises to revolutionize how we design molecules and approach therapeutic challenges.[5] As we look ahead, AI's role in drug discovery is poised to transition from an auxiliary tool to a central figure in the design, testing, and optimization of new compounds. This shift is predicated on AI's ability to process vast datasets, drawing insights that would be unattainable to human researchers alone. The integration of AI with cutting-edge experimental techniques will enable the design of molecules with unprecedented specificity and efficacy, reducing the time and cost associated with bringing new drugs to market.

ENHANCED PREDICTIVE MODELS & PERSONALIZED MEDICINE

The evolution of AI models, fueled by richer and more comprehensive datasets, will lead to more accurate predictions of drug behavior and interactions within the human body. This advancement holds the key to personalized medicine, where treatments can be tailored to the genetic makeup of individual patients.[6] AI's ability to sift through genetic information and correlate it with drug responses will open new avenues for customized therapies, making treatments more effective and reducing the incidence of adverse reactions.

NAVIGATING THE COMPLEXITY OF BIOLOGICAL SYSTEMS

As AI technologies mature, their application will extend beyond traditional drug design to explore complex biological systems and disease pathways. AI models will be instrumental in uncovering novel targets and understanding the multifaceted nature of diseases like oncology, CNS, cardiovascular, and autoimmune disorders, to name a few. By simulating the interactions within these systems, AI will identify new therapeutic opportunities and guide the development of drugs that can modulate disease processes more effectively.

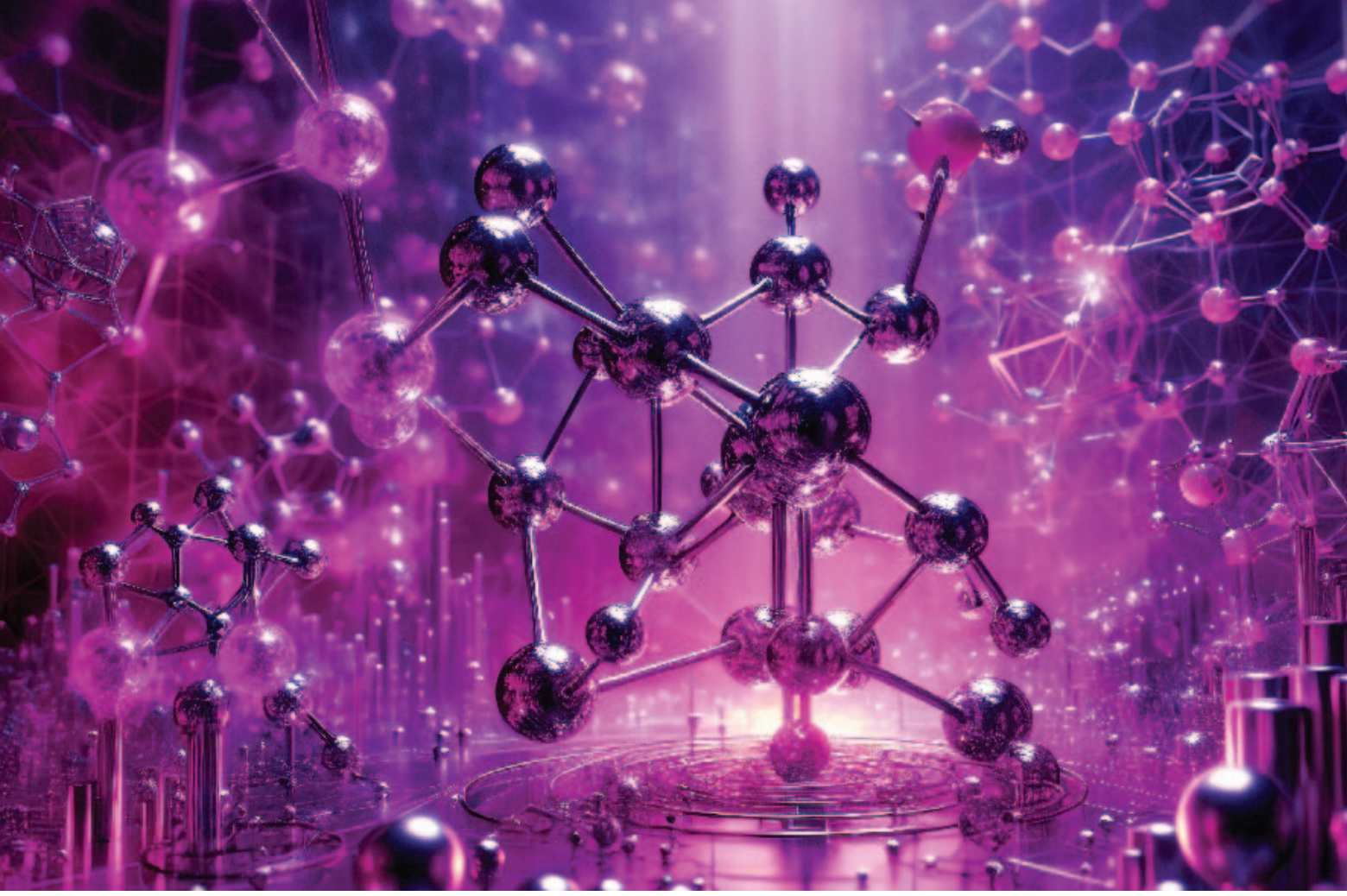
THE GROWING SYNERGY OF AI & EXPERIMENTAL VALIDATION

The future will also see a deeper integration of AI with experimental validation, creating a seamless feedback loop that accelerates the discovery process. This synergy will ensure that AI-designed molecules are not only theoretically effective but also validated through empirical data. The continuous exchange of data between AI models and laboratory results will refine AI predictions, making the drug discovery process more efficient and reliable.

Additionally, this integration will facilitate the development of more sophisticated AI algorithms, thereby enhancing the predictive accuracy for drug efficacy and safety profiles before clinical trials commence. Furthermore, the democratization of drug discovery through AI enables all levels of research to leverage cutting-edge research tools, broadening the scope of innovation and potentially reducing the time and cost to market for new treatments.

SUMMARIZING WHAT'S TO COME

The horizon for AI in drug discovery is expansive, promising to streamline the discovery of new therapies and usher in an era of personalized, effective, and accessible treatments. As AI and experimental science fuse, the drug



discovery landscape will be transformed, with Logica fully equipped and focused on leading the charge toward this exciting future. This shift is expected to accelerate innovation, diversify the pipeline of drug candidates, and potentially reduce the overall cost of bringing new treatments to market, marking a significant step forward in making advanced drug discovery tools accessible to a broader range of researchers and companies.

LOGICA: LEADING THE AI REVOLUTION IN DRUG DISCOVERY

Logica, a collaboration between Charles River and Valo Health, is an example that exemplifies the possibilities for AI's integration into drug discovery. Under a team of drug discovery veterans, Logica is pioneering a new approach. By marrying AI with "wet science" data, Logica is not only accelerating the discovery process, but also intends to bolster the success rates of advanceable drug leads.

AI in drug discovery represents a paradigm shift, not just in how we approach the science of finding new medicines but in how we envision the future of pharmaceutical research. At Logica, we're not just using AI; we're integrating it with the invaluable insights provided by wet lab data to create a seamless, iterative process. This approach isn't engineered to just speed up discovery; it's designed to enrich it, ensuring that every step of the process is informed by the most accurate, up-to-date data available. We're excited for what's becoming possible in drug discovery — and we're excited to be part of proving that when AI and human expertise combine, the potential is limitless.

EMBRACING THE AI REVOLUTION: A NEW ERA IN DRUG DISCOVERY

As we stand on the brink of a new era in drug discovery, the integration of artificial intelligence (AI) with experimental data heralds a transformative shift in how we approach the creation of new medicines. This revolution, characterized by a seamless blend of computational power and biological insight, is not merely about enhancing the efficiency of drug discovery processes; it's about fundamentally redefining what is possible in the quest to treat and cure diseases. The burgeoning field of digital biology, powered by AI, is poised to turn biology

into an engineering discipline, opening unprecedented opportunities for drug discovery.[7] Furthermore, the rapid advancement of AI-designed drugs through both the discovery and preclinical stages, as demonstrated by recent clinical trials, underscores AI's potential to significantly accelerate the drug development process. Logica, through its pioneering efforts, exemplifies the potential of this synergy, driving forward with innovations that promise to reshape the landscape of pharmaceutical research and development.

The journey of AI in drug discovery, from its nascent integration to becoming an indispensable tool, illustrates a path filled with challenges, learning, and ultimately, immense rewards. The ability of AI to sift through and make sense of vast datasets, to predict outcomes with increasing accuracy, and to uncover insights that elude human cognition, is a testament to the power of this technology. Yet, it is the marriage of AI with the rich, nuanced data from experimental research that truly unlocks its potential. This partnership does not replace the human element but rather enhances it, allowing scientists to explore new hypotheses, to test the boundaries of current knowledge, and to accelerate the pace at which new treatments can be developed and brought to market.

Looking to the future, the promise of AI in drug discovery is boundless. With each advancement in AI technology and each new dataset generated from experimental research, we edge closer to a world where drug discovery is more predictive, personalized, and potent. The role of initiatives like Logica becomes increasingly crucial as we navigate this uncharted territory, blending the art of science with the precision of algorithms to forge new paths in healthcare. As we embrace the AI revolution, we do so with the knowledge that we are not just witnessing a change in how we discover drugs but are participating in a historic moment that will define the future of medicine. ◆

REFERENCES

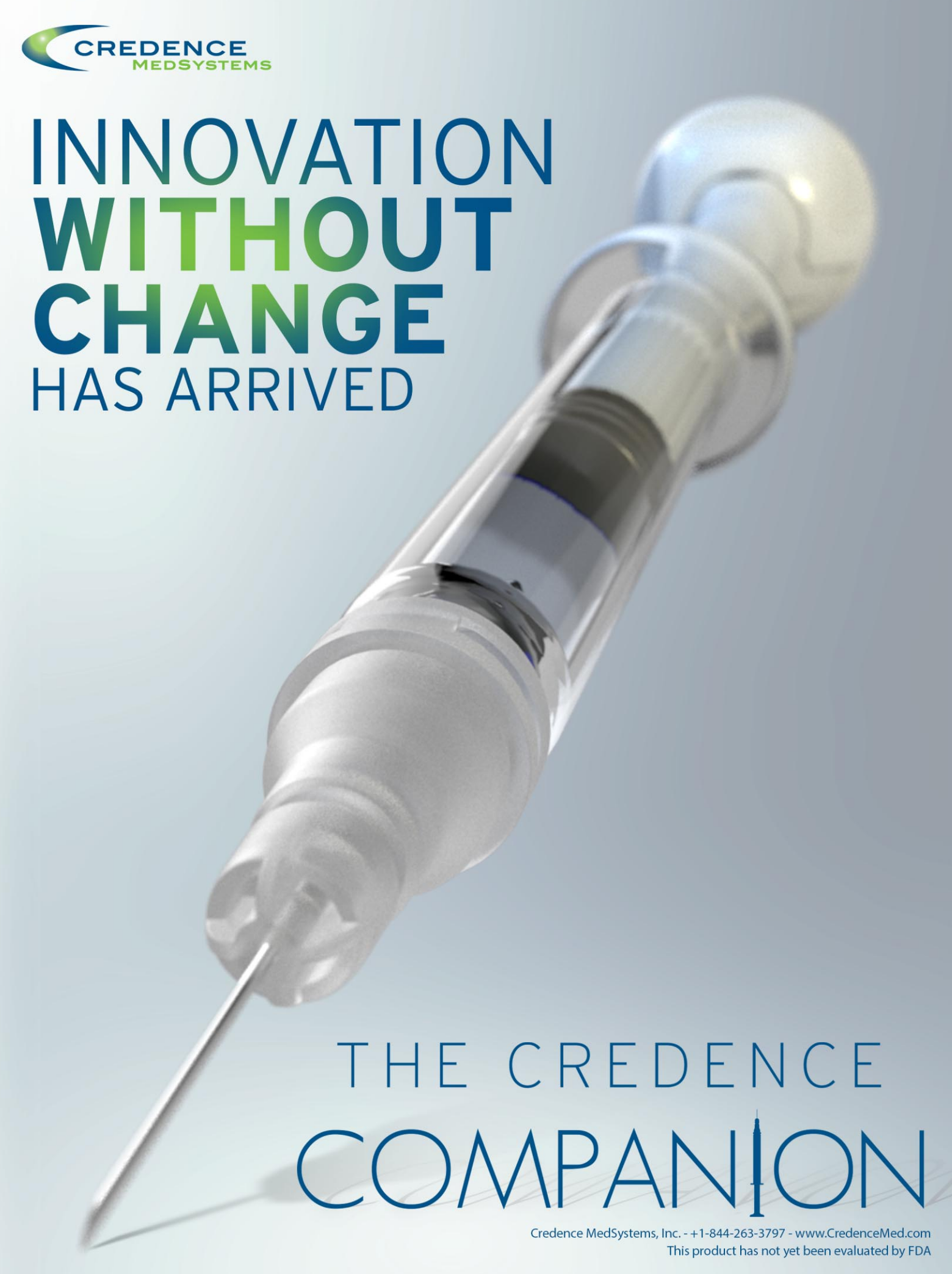
1. Fleming, N. How artificial intelligence is changing drug discovery. Nature. Published 2018 May 30.
2. Ayers, M., et al. Adopting AI in Drug Discovery. Boston Consulting Group. Published 2022 March 29.
3. Blanco-Gonzalez, A., et al. The Role of AI in Drug Discovery: Challenges, Opportunities, and Strategies. Pharmaceuticals. Published 2023 June 18. 18;16(6):891.
4. Barzilay, R., et al. The race for a cure. Royal Society of Chemistry. Published 2020 June 3.
5. Jiménez-Luna, J., et al. Artificial intelligence in drug discovery: recent advances and future perspectives. Expert Opinion on Drug Discovery. Published 2021 April 2.
6. Khatami, S.G., et al. Using predictive machine learning models for drug response simulation by calibrating patient-specific pathway signatures. Nature. Published 2021 October 27.
7. Regalado, A. An AI-driven "factory of drugs" claims to have hit a big milestone. MIT Technology Review. Published 2024 March 20.

BIOGRAPHY

Dr. Emilio Cordova, Executive Director of Logica, Charles River, has served in this position since June 2023. Prior to his appointment at Logica, he was CEO of SAMDI Tech, Inc. for 8 years, culminating in the successful acquisition by Charles River in 2023. He brings over 25 years of management and executive experience in contract research. Throughout his career, he held leadership positions in sales, marketing, and business development including positions at Worldwide Clinical Trials, Bioanalytical Systems, Inc., and AIT Bioscience. He earned his Ph.D. from the University of Miami and his MBA from Purdue University's Krannert School of Management. In addition, he completed an NIH post-doctoral fellow appointment at Harvard University under the guidance of Dr. George Whitesides.

CREDENCE MEDSYSTEMS

INNOVATION WITHOUT CHANGE HAS ARRIVED



THE CREDENCE COMPANION

Credence MedSystems, Inc. - +1-844-263-3797 - www.CredenceMed.com

This product has not yet been evaluated by FDA

FORMULATION DEVELOPMENT

Solubility-Enhancing Technologies in Pharmaceutical Development, a Mini-Review

By: Timothy Pas, PhD, and Vincent Levet, PhD

INTRODUCTION

The Biopharmaceutics Classification System (BCS) and Developability Classification System (DCS) have been used since the 1990s to classify drugs into different categories based on their permeability or solubility. A frequent challenge in contemporary drug development lies in the low aqueous solubility exhibited by a significant proportion of emerging Active Pharmaceutical Ingredients (APIs), thereby negatively affecting their absorption following oral administration.

Most of the drugs in development fall into categories in which solubility poses challenges, particularly when aiming for oral administration. In the initial stages of drug development, liquid formulations are typically preferred due to their ease of modification and adaptability. However, as the development process progresses into later phases, the formulation strategy needs to shift toward more user-friendly formats, such as tablets or capsules. This transition is driven by factors such as ease of administration, patient compliance, and stability of the drug product.

To tackle these challenges, different solubility-enhancing technologies can be used by developers. With different advantages and drawbacks, linked to payload, manufacturability, tolerability, and physical and chemical stability, effectively navigating solubility-enhancing solutions is multifaceted.

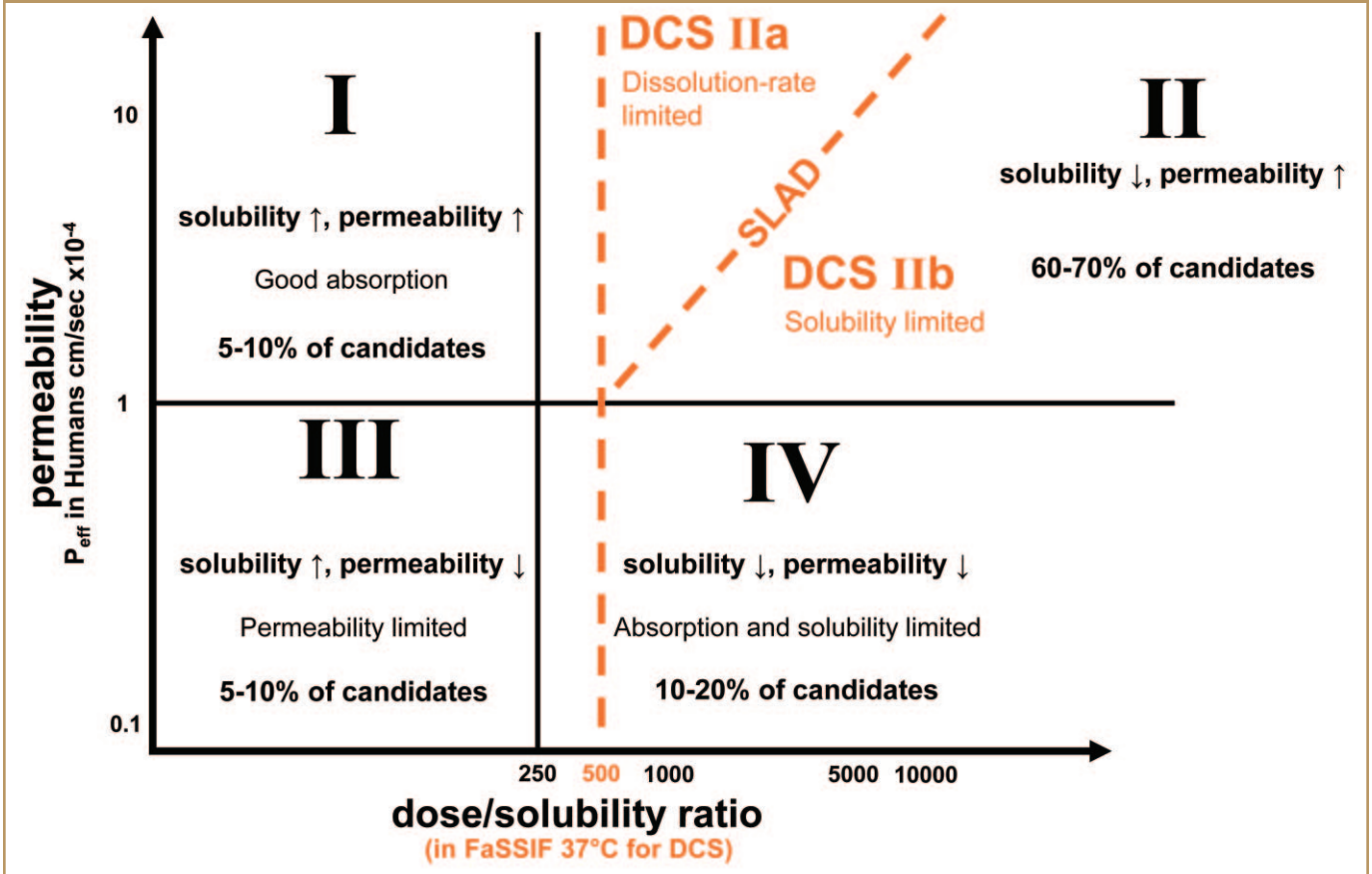
UNDERSTANDING THE BIOPHARMACEUTICS & DEVELOPABILITY CLASSIFICATION SYSTEMS

The BCS was introduced in 1995 and classifies APIs into four distinct classes based on their solubility and permeability characteristics: Class I (high solubility, high permeability), Class II (low solubility, high permeability), Class III (high solubility, low permeability), and Class IV (low solubility, low permeability) providing a guideline for developers to predict the oral bioavailability of a drug.[1,2]

In reality, most of the absorption of oral drugs takes place in the small intestine, where drugs must first solubilize into gastrointestinal (GI) fluids, to then cross GI membranes, to reach the systemic circulation and eventually generate the intended therapeutic effect. The DCS was introduced in 2010 as a revised version of the BCS. These modified guidelines recognize that certain drug candidates classified in BCS Class II exhibit unique challenges beyond solubility, influencing their delivery, focusing in particular on their behaviour in the GI tract. It takes the following into account:

- The use of more biorelevant media with concomitant more realistic volumes.
- The implementation of a solubility-limited absorbable dose (SLAD) because, at least for BCS Class II, solubility and permeability are compensatory.
- The expression of the dissolution rate as a target drug particle size rather than as a dose/solubility ratio.

FIGURE 1



BCS and DCS, adapted from Nikolakakis et al[4] and Samineni et al[5]. SLAD: Solubility-limited absorbable dose. Peff: Predicted permeability in humans.

The majority of recent drug candidates exhibiting low aqueous solubility fall into BCS Class II, posing a substantial difficulty in achieving optimal absorption after administration. A differentiation between those belonging to DCS Class IIa (Dissolution-rate limited) and those in Class IIb (Solubility-limited) can be made (Figure 1). Because of this, the integration of solubility-enhancing technologies has become central in pharmaceutical development strategies. The selection of a formulation approach necessitates thoughtful evaluation of various parameters, including API solubility, not only in aqueous media and representative dissolution mediums, but also in alternative solvents for administration or for the manufacturing steps. This assessment should also encompass considerations related to the physicochemical profile, permeability, and intended dose, as well as factors pertaining to manufacturing.[3]

EXPLORING SOLUBILITY-ENHANCING TECHNOLOGIES FOR DRUG SOLUBILITY

A wide variety of technologies (Table 1) exist to tackle poor solubility, and in general, these focus on optimizing the API itself (eg, pro-drug formation, use of different salts, co-crystallization) or by means of various formulation approaches through for instance optimization of API solubility in aqueous medium (pH-shift, surfactant-addition), suspensions associated with particle size reduction (nanosuspensions), predissolved forms (lipid-based and related systems, cyclodextrin complexes, co-solvents) or use high-energy solid forms to generate supersaturation (amorphous solid dispersions).

In preclinical toxicity testing, achieving systemic exposures at doses significantly exceeding the anticipated clinical dose is necessary, emphasizing the need for higher solubility. To reach these elevated doses, oral gavage administration is the most direct and in rodent studies, often the only option. In the early phases of clinical studies, particularly in Phase 1, clinicians prefer dosage forms that offer flexibility to cover a broad dosing range. Considering these factors of dose and administration flexibility, solubility-enhancing formulations in early development are typically liquid forms. In this respect, solutions or suspensions allow easy dilution to lower

TABLE 1

Technology	Performance Driven By	Payload	Manufacturing Complexity	Tolerability	Physical Stability	Chemical Stability
Nanocrystals and nanosuspensions	Dissolution rate enhancement Nanocrystal size, surface area, paracellular transport	High-payloads (20-30%) for physicochemically diverse APIs	High	Well tolerated	Some development required to prevent particle growth (= Ostwald ripening) during storage	Generally good as API is crystalline
Lipid-surfactant cosolvent based systems (e.g. liposomes, microemulsions, Self-emulsifying drug delivery systems (SEDDS), Solid lipid nanoparticles (SLN), Nanostructured lipid carriers (NLC)	Avoidance of dissolution process Enhanced solubility in GI fluids Lymphatic uptake	Depends highly on API solubility in excipients and on the format. May not be suitable for high-melting point APIs	Low to High	Some excipients may cause side effects at higher doses As liquid form: poor palatability	No concerns as API is in lipidic solution, Higher instability expected for lipid particles formats, Precipitation if API can partition to aqueous phase	Worse relative to crystalline form as API is in solution. Multiple excipient- derived degradation pathways possible.
Cyclodextrin complexes	Avoidance of dissolution process. Enhanced solubility in GI fluids	Depends highly on complexation efficiency, but is rarely in excess of 5%	Low	Well tolerated	High, API in solution	Worse relative to crystalline forms as API in solution
Amorphous solid dispersions	Supersaturation	High payloads may be achievable in polymer matrix (20-50%) but ca. 5-fold dilution required when dosing as a suspension (for PK studies). Most of the time administered as capsules or tablets.	High	Well tolerated	Poor, a lot of development necessary to prevent crystallisation during storage	Worse relative to crystalline forms as higher energetic form

Overview of solubility-enhancing technologies and their respective driving selection parameters.

concentrations or variable volumes for achieving diverse doses.[6]

Practically all widely used solubility-enhancing technologies, such as nanosuspensions, lipid-based systems, and cyclodextrin complexes, can be readily processed into liquid formulations. Amorphous solid dispersions, despite being solid products, can be formulated into a suspension by dispersing them in an aqueous or alternative vehicle shortly before administration (with precautions in place to ensure this dispersion process doesn't adversely impact its performance as dissolution of the amorphous API has already started).[3]

UTILIZING NANOSUSPENSIONS TO IMPROVE DRUG SOLUBILITY

Nanosuspensions represent an attractive way to improve bioavailability of poorly soluble drugs, by enhancing the dissolution rate of APIs through an increased surface area, enabling paracellular transport or lymphatic transport. Nanosuspensions can generally facilitate high payloads and require low excipient concentrations. However, they also exhibit challenges related to physical stability, such as crystal growth (also known as Ostwald ripening) and agglomeration, especially during manufacturing or long-term storage.

From a manufacturing point of view, both bottom-up and top-down approaches are possible. The bottom-up approach involves the controlled precipitation of the API from a (non-aqueous) solution or melts into a non-solvent, often in parallel with high-energy methods (e.g. high-shear mixing or ultrasonication), to produce nanoparticles. This bottom-up approach enables precise control over particle size distribution during the nanoparticle formation process, contributing to a better shape and size uniformity (ie, a lower Polydispersity Index) and increased physical stability.

Alternatively, the top-down approach involves applying mechanical forces to break down larger API particles into nano-sized ones using techniques like high-pressure homogenization or through wet or dry (ie, jet milling) techniques using coarse materials. Top-down is generally considered more scalable and adaptable to a larger variety of APIs, as it does not rely on solubilizing the API at any point during manufacturing.

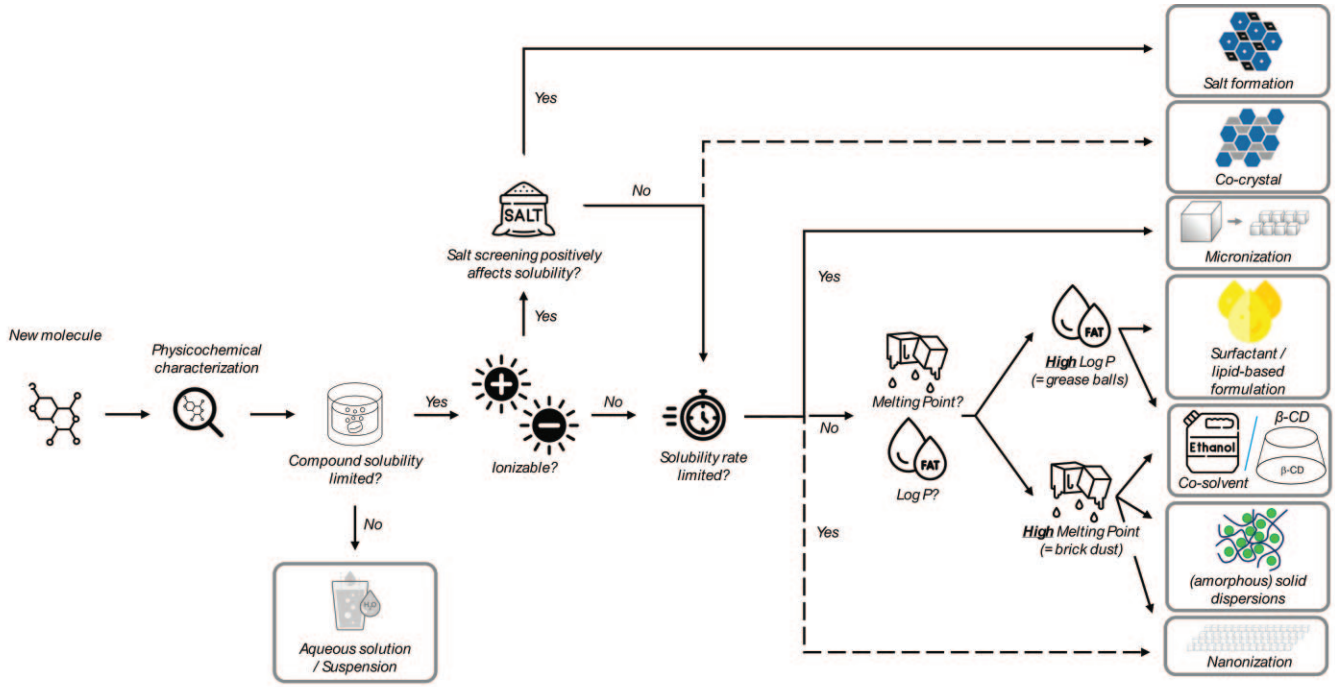
In the formulation development stages, the objective is to ensure the long-term stability of nanosuspensions, and during this process, the identification of an effective excipient mix (eg, surfactants, polymers like polyvinylpyrrolidone) is undertaken to manage, in particular, correct size-reduction and undesirable particle growth.

The performance of nanosuspensions predominantly relies on their dissolution rate enhancement. While suitable for a diverse range of drug candidates, they may prove inadequate when formulating exceptionally challenging molecules, leading to considerations of alternative strategies, such as lipid-based systems or amorphous solid dispersions.[7]

HARNESSING LIPID-BASED FORMULATIONS

The use of lipid-based and related formulations, including lipid solutions, emulsions, and self-emulsifying (micro or nano) drug delivery systems (SEDDS, SNEDDS, SMEDDS), and solutions employing co-solvents and surfactants, ad-

FIGURE 2



Solubility-enabling techniques decision tree. Note: Salt formation and co-crystals are rather new chemical entities than formulation technologies.

dress challenges associated with the slow dissolution of APIs from the crystalline form in aqueous media. This approach presents the API to GI fluids after administration in a pre-dissolved state in lipophilic materials, enhancing solubility and absorption, and eventually improving bioavailability. SEDDS, for instance, are a sort of (semi-)solid or liquid formulation composed of the following:

- The API,
- Oils (medium-chain triglycerides e.g. caprylic acid, capric acid, lauric acid; long-chain triglycerides, eg, soybean oil, sunflower oil, mixes of medium and long-chain triglycerides; others, eg, isopropyl myristate),
- Waxes/fats (eg, gelucire),
- Surfactants (eg, sodium lauryl sulfate, sorbitan monostearate, lecithin),
- Humectants (eg, glycerol, sorbitol, polyethylene glycol/PEG), and
- Co-solvents on an accasional basis (eg, ethanol).

These SEDDS form in situ emulsions with moderate stirring and dilution by water-phase of GI fluids directly after administration in the GI tract. As such, they can increase the solubility and bioavailability of poorly soluble APIs.

Challenges associated with this approach include potential limitations on achievable payloads, particularly for APIs with high melting points or with equally low solubility profiles in lipids. For SEDDS for instance, high payloads can only be achieved if the API demonstrates a remarkable solubility in one of the excipients used (eg, oil or surfactant). Moreover, lipid formulations often incorporate excipients containing reactive molecules or impurities (eg, esters, formaldehyde, peroxides), posing risks of chemical degradation such as oxidation, acylation, and transacylation, which can be critical for the stability and safety of the formulation.

These stability issues can be mitigated by the formulators through careful choice of excipients, or by presenting the API in a dried form, to be reconstituted with the lipidic vehicle right before administration (eg, two vials presentation). Risks of precipitation upon dilution *in vivo* or of poor release from the emulsified systems also exist and should not be overlooked as they could impact bioavailability. Finally, a major drawback of these formulations is their poor palatability and the taste of some excipients (eg, surfactants). After early phase studies where this is often inevitable, taste-maskers (eg, sweeteners, flavorants) or liquid-filled capsules (eg, soft gels or hard caps) are often chosen.[8,9]

MAKING CYCLODEXTRIN COMPLEXES TO PROMOTE SOLUBILITY

Cyclodextrins have been widely used as pharmaceutical excipients since the 1980s due to manufacturing improvements. They are oligosaccharides composed of between 6-8 α-(1,4) linked

α-D-glucopyranose units arranged in a ring. Their inner cavity is therefore lipophilic, while their outer surface is hydrophilic, which makes them soluble in water, and able to "shield" lipophilic API from the aqueous media, enhancing the API solubility.

Hydrophilic derivatives of β-cyclodextrins, such as hydroxypropyl-β-cyclodextrin (HP-β-CD), are very well characterized and have low toxicity (ie, up to approx. 28 g β-CD can be dosed per day). Cyclodextrins offer enhanced stability against dilution-induced precipitation, setting them apart from alternative solubilization techniques like cosolvents. Their ability to efficiently and specifically bind with the API enhances solubility in aqueous media in a targeted and effective manner, providing a tailored solution for specific drug compounds with high complexation profiles.

However, cyclodextrin-based formulations typically face payload restrictions, rarely exceeding 5%. One significant disadvantage arises in the context of toxicity studies, particularly in rodents. The payload restrictions associated with cyclodextrins may limit their extensive use in such studies in which higher drug concentrations are often necessary for accurate assessments.This limitation can impact their applicability. Additionally, the cost-effectiveness of cyclodextrin-based solubilization should be carefully evaluated, considering their very high cost.

Considering scalability is crucial for the broader adoption of cyclodextrin-based solubilization processes. Furthermore, understanding how frequently this approach is applied in contemporary pharmaceutical development strategies provides insights into its practicality on a larger scale.[10-12]

PRODUCING AMORPHOUS SOLID DISPERSIONS

Amorphous solid dispersions (ASDs) are based on the molecular dispersion of the API, which corresponds to the disruption of the crystalline lattice, into an inert carrier such that less energy is required to promote their dissolution. As a result, ASDs present an interesting solution in drug development of poorly soluble APIs offering a significant advantage in circumventing bioavailability issues. The amorphous state of the dispersion enhances the rate and the extent of dissolution of the API, as it enables and extends supersaturation (a so-called spring- and parachute effect) in the GI tract, enhancing bioavailability.

However, ASDs manufacturability is often complex. The production process requires the use of either organic solvents (e.g. in spray drying) or high temperatures (e.g. in hot-melt extrusion), introducing challenges related to API degradation, process control, reproducibility, and consistency. This can potentially impact the ability to go to large-scale manufacturing.

A key challenge in the development of ASDs is stability, both chemically and physically, upon storage. The inherent instability of the amorphous state makes it susceptible to transitioning into a crystalline form over time. Preventing and reliably detecting crystallization therefore becomes a critical aspect of the development process. Prevention starts from a thorough ASD formulation and excipient selection process (eg, polymers, surfactants), as they can help to stabilize the amorphous state by interacting with the API. Other parameters, such as controlling the storage conditions (ie, temperature and humidity), are also key in that aspect. In addition, having the correct tools at your disposal to assess the solid state of these systems enables early detection of the onset of crystallization and hence high-quality selection of concepts.[13]

SUMMARY

In summary, addressing the challenge of low aqueous solubility in drug development requires a comprehensive evaluation of API properties and solubility-enhancing technologies (Figure 2). Beyond increasing solubility, factors like payload, manufacturability, administration convenience, and stability play pivotal roles in shaping strategic decisions during early drug development.

As drug development advances into later phases, the selected formulation strategy also needs to evolve from liquid formulations, valuable in the early stages, to tablets or capsules.

Among the array of solubility-enabling technologies, nanosuspensions, lipid-based formulations, cyclodextrins, and ASDs each present distinct advantages and challenges. The choice of technology will depend on the unique characteristics of the drug candidate and the requirements of the development phase. ◆

REFERENCES

1. Amidon G, Lennernäs H, Shah V, Crison J. A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. Pharm res. 1995 Mar;12(3):413-20. doi: 10.1023/a:1016212804288.
2. FDA, M9 Biopharmaceutics Classification System - Guidance for Industry, 2021.
3. Butler J, Dressman J. The Developability Classification System: Application of Biopharmaceutics Concepts to J Pharm Sci. 2010 Dec;99(12):4940-54. doi: 10.1002/jps.22217.
4. Nikolakakis I, Partheniadis I. Self-Emulsifying Granules and Pellets: Composition and Formation Mechanisms for Instant or Controlled Release. Pharmaceutics. 2017 Nov 3;9(4):50. doi: 10.3390/pharmaceutics9040050.
5. Samineni R, Chimakurthy J, Konidala, S. Emerging Role of Biopharmaceutical Classification and Biopharmaceutical Drug Disposition System in Dosage form Development: A Systematic Review. Turk J Pharm Sci. 2022 Dec; 19(6): 706–713.
6. Buckley S, Frank K., Fricker G, Brandl M. Biopharmaceutical classification of poorly soluble drugs with respect to "enabling formulations". Eur

J Pharm Sci. 2013 Sep 27;50(1):8-16. doi: 10.1016/j.ejps.2013.04.002.
7. Patel V, Agrawal Y. Nanosuspensions: An approach to enhance solubility of drugs. J Adv Pharm Technol Res. 2011 Apr-Jun; 2(2): 81–87. doi: 10.4103/2231-4040.82950.
8. Zhu Y, Ye J, Zhang Q. Self-emulsifying Drug Delivery System Improve Oral Bioavailability: Role of Excipients and Physico-chemical characterization. Pharm Nanotechnol. 2020;8(4):290-301. doi: 10.2174/2211738508666200811104240.
9. Salawi A. Self-emulsifying drug delivery systems: a novel approach to deliver drugs. Drug Deliv. 2022 Dec;29(1):1811-1823. doi: 10.1080/10717544.2022.2083724.
10. Jambhekar S, Breen P. Cyclodextrins in pharmaceutical formulation I: Structure and physicochemical properties, formation of complexes, and types of complex. Drug Discov Today . 2016 Feb;21(2):356-62. doi: 10.1016/j.drudis.2015.11.017.
11. Kiss T, Fenyvesi F, Bácskay I, Váradi J, Fenyvesi E, Iványi R, Szente L, Tósaki A, Vecsernyés M. Evaluation of the cytotoxicity of B-cyclodextrin derivatives: Evidence for the role of cholesterol extraction. Eur J Pharm Sci . 2010 Jul 11;40(4):376-80. doi: 10.1016/j.ejps.2010.04.014.
12. Fenyvesi F, Phuong Nguyen T, Haimhoffer A, Rusznyák A, Vasvári G, Bácskay I, Vecsernyés M, Ignat SR, Dinescu S, Costache M, Ciceu A, Hermenean A, Váradi J. Cyclodextrin Complexation Improves the Solubility and Caco-2 Permeability of Chrysin. Materials (Basel) . 2020 Aug 16;13(16):3618. doi: 10.3390/ma13163618.
13. Bhujbal S, Mitra B, Jain U, Gong Y, Agrawal A, Karki S, Taylor L, Kumar S, Zhou S. Pharmaceutical amorphous solid dispersion: A review of manufacturing strategies. Acta Pharm Sin B . 2021 Aug;11(8):2505-2536. doi: 10.1016/j.apsb.2021.05.014.

BIOGRAPHIES

Dr. Vincent Levet is Director, Formulation Development and Production, Ardena. He earned his MPharm and PhD in Pharmaceutical Technology from ULB, Belgium, with an MBA from Quantic, USA. His expertise spans from developing sustained-release solid lipid microparticles for lung cancer treatment to leading formulation teams at GSK Vaccines and Lonza Drug Product Services. Since September 2023, he has directed Formulation Development and GMP Production at Ardena, guiding a diverse team to excellence in early-phase clinical trials.

Dr. Timothy Pas is Group Leader, Formulation Development and Production, Ardena. He earned his Master's in Pharmacy and his PhD in Pharmaceutical Technology from KU Leuven, specializing in enabling technologies and galenic principles. Transitioning to industry at Ardena, he progressed from Scientist to Group Leader, excelling in solid and liquid oral formulations, enabling technologies, and galenic presentations. Leading a talented team, he drives drug development and GMP manufacturing of early stage clinical materials, showcasing Ardena's commitment to pharmaceutical innovation.

Why PharmaCircle?

Since 2003, PharmaCircle has been providing clients with the integrated data, powerful analysis tools and industry knowledge needed to solve complex, real world challenges in product development and innovation.

PHARMACIRCLE™

www.pharmacircle.com

Pipeline & Products Intelligence

Business Intelligence & Prospecting Tools

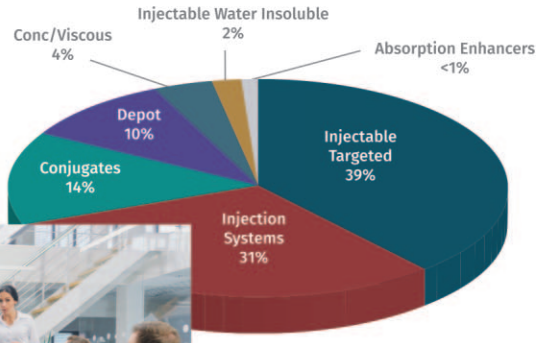
Research & Development Analysis Tools

Regulatory Databases & Documents

View Formulation and Component Details

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

Evaluate New and Promising Technologies



Injectable Drug Delivery Technologies

Screen Potential Partnering and Investment Opportunities

Assess Development Pipelines and The Competitive Landscape

PHARMACIRCLE™

Schedule Your Demo

PharmaCircle serves commercial and emerging stage life sciences companies and suppliers from around the world. See how we can help you.

www.pharmacircle.com

Special Feature

Injection Devices: From Pens & Autoinjectors to Pills, Sprays & Capsules, Injections Become More Efficient

By: Cindy H. Dubin, Contributor

The pharma community has made incredible advancements in developing injectable devices that are less painful, ensure precise drug delivery, reduce injection frequency, and integrate with digital health technologies – all of which are important for patients treating chronic diseases. As the comfort level for patients to self-administer medication rises, so too does the global injection drug delivery market. Estimated to be valued at $757.06 billion this year, the market is projected to reach 1,630.73 billion by 2033, according to Nova One Advisor.

While most of the innovation witnessed is in patient-centric devices like autoinjectors and pen devices, there are exciting alternatives hitting the market. For example, the Food and Drug Administration just approved ARS Pharmaceuticals' neffy epinephrine nasal spray for severe allergic reactions. This makes it the first non-needle epinephrine treatment available in the United States for adults and older kids with food, sting or drug allergies. In a statement, ARS Pharma's president and CEO said: "This approval marks a watershed

Vetter invests in robots like YuMi and other automation and digitization initiatives to provide top-of-the-line performance for customers.

moment in addressing an unmet medical need for people with Type I allergies. The sprayer is a treatment alternative that avoids the need to inject epinephrine with a needle."

Avoiding needles is the reason why oral drug delivery remains the most widely used route of delivery. Companies like Rani Therapeutics recognize this and developed what it believes is disruptive technology for the oral delivery of biologics: the RaniPill Platform. The RaniPill Capsule is a robotic pill that moves fully intact through the stomach and reaches the intestine to deliver drug via transenteric injection. In February, Rani announced positive topline results from its Phase 1 clinical study of RT-111, a RaniPill capsule containing an ustekinumab biosimilar, CT-P43. In the study, RT-111 was well-tolerated and delivered ustekinumab with high bioavailability.

"We are highly encouraged by the positive results from our Phase 1 study for RT-111 – our third successfully completed Phase 1 trial using RaniPill technology," said Talat Imran, Chief Executive Officer of Rani in a press release. "To our knowledge, RT-111 is the first ever oral monoclonal antibody to achieve high bioavailability in humans. These data provide clinical validation of our ability to successfully transform an injectable large molecule into an oral pill. Specifically for this program, we believe RT-111 has the potential to offer a highly differentiated dosing regimen for patients with psoriasis compared to both injectable biologics and oral small molecules and peptides."

Researchers have developed an injectable capsule, known as L-SOMA engineered with an advanced driving and delivery mechanism. This system facilitates the encapsulation of both small-molecule drugs and large-molecule drugs, such as monoclonal antibodies, while doubling the drug loading capacity. L-SOMA can achieve a peak plasma concentration akin to subcutaneous injection standards within a 30-minute post-administration, and can reach bioavailability of 80% within a few hours. Alex Abramson, Assistant Professor at Georgia Institute of Technology, explains that to deliver the drug, the L-SOMA uses a staged and sequence controlled multi-spring actuation system that injects a hypodermic needle beneath the gastric mucosa and thereupon delivers 80µL of liquid drug formulation into the submucosal space. The L-SOMA's actuation mechanism is located on the shell of the device, eliminating the need for gastric fluid to enter the pill and be in contact with the loaded drug before injection. A dissolving pellet, accessed through a hole on the top of the pill, holds an injection molded needle hub in place using a latching mechanism. Over time, this pellet dissolves. Once actuated, the L-SOMA first inserts a needle into the tissue to a defined distance using an excess of force. Then it uses a second spring to push down on a plunger that drives the liquid drug formulation through the needle and into the gastric submucosa. Two membranes seal off the dose storage area and prevent leakage as the plunger pushes the liquid through a side hole in the needle and out via the needle's tip. By decoupling the needle insertion from the liquid injection, the device achieves delivery of its entire dose deep within the tissue instead of releasing the dose as the needle moves through the tissue. He says this staged injection system prevents any of the dose from expelling into the gastric fluid where it could be degraded.

This exclusive *Drug Development & Delivery* annual report highlights other innovative and promising injection technologies that are ever more user friendly, versatile, precise, and life- saving.

ApiJect: Prefilled Autoinjector Overcomes Prohibitive Pricing

Autoinjectors and other take-home injection delivery devices are removing barriers for patient access to the medicine they need. ApiJect's mission is to make injectable medicines and vaccines safe and accessible to everyone. The company helps pharmaceutical companies design rapidly scalable, affordable, easy to use, and sustainable drug delivery systems.

The ApiJect platform, for example, creates prefilled injection devices by bringing together Blow-Fill-Seal (BFS) advanced aseptic drug packaging with attachable drug delivery components. This allows the ApiJect platform to create safe, affordable,

The prefilled ApiJect injector is priced to enable access to more people.

and easy-to-use prefilled drug delivery systems.

Joseph Wojcik, MBA, PMP, Senior Director, Pharmaceutical Sciences, ApiJect, explains that in high-income countries, autoinjectors are popular because of their convenience and their price point is not prohibitive when compared to visiting a hospital or clinic. However, in a low- or middle-income country, the autoinjector is likely more expensive than the clinic visit (and certainly more expensive than at-home use of a vial and syringe).

"Its high price point significantly decreases its demand, which in-turn reduces access for those who can afford it," he says. "The ApiJect platform can transform this situation by providing the safety and ease-of-use of a prefilled format at a price point that more people can afford across the globe – helping to increase access to more injectables using market forces."

ApiJect is currently working with a client to solve a problem related to use and access of their injectable drug product in low- and middle-income countries. By leveraging the ApiJect technology platform and ApiJect's Global Health, Device Design, and Product Development teams, ApiJect has collaborated with this client to develop a solution that meets the specific device delivery needs of their drug product and addresses "Last Mile" issues that limit access to critical medicines, says Mr. Wojcik.

Artcraft Health: No-Fail Autoinjector Training

Known for their ease of use, autoinjectors are quickly becoming the most popular type of self-injection device because they are pre-dosed and straightforward for patients to learn, which reduces the risk of user error.

Artcraft Health is a full-service health education agency that partners with pharma, biotech healthcare service, and medical device companies. Artcraft has long served the injectables market with demonstration device training, particularly with autoinjectors, for which there is an ongoing need to ensure successful patient onboarding.

"The most critical part of autoinjector use is patient training," says Marty Mason, Senior Director of Demonstration and Training Devices at Artcraft Health. "An autoinjector is only as good as the training that accompanies it," he says.

To meet the biggest unmet need of the autoinjector market, Artcraft has recently developed the first autoinjector training device that delivers no-fail training, even if the device itself fails. Artcraft's demoX™ training device – the industry's first electronic autoinjector training device – delivers no-fail training by using pre-programmed movements to replicate the functions of a commercial autoinjector with zero-motion variability, he explains.

If demoX starts to fail due to loss of power, a battery indicator light prompts the clinician to give the device a 5-minute recharge to restore its no-fail performance, so clinicians never experience a training failure – even if the device itself fails.

According to Mr. Mason, "demoX was created to solve the problem of autoinjector training devices that don't last as long as projected and exhibit problematic variations in key functions such as plunger drop and in the sound of the audio click. As a fully rechargeable electromechanical device, demoX avoids the rapid wear and tear that befall traditional devices and eliminates the motion and timing variability that has become a sore point for the industry. In fact, demoX is engineered to last five times longer than previous generations of training devices." As an added benefit for clients, the demoX device has an internal counter that tells sales reps how many times the HCP has used the device.

In addition to the launch of demoX, Artcraft Health has deep portfolio experience in connected and wearable devices, having created electromechanical training devices for several injection systems. The accuDemo technology, launched last year, is a training platform that eliminates 100% of user errors in every onboarding session, says Mr. Mason.

BD: Range of Devices Deliver Complex Biologics

A broad portfolio of drug delivery systems designed for high-volume and complex biologics is available from BD and are designed to be intuitive, reliable and enhance the overall patient experience. The BD Effivax™ Glass Prefillable Syringe, BD Libertas™ Wearable Injector, and the BD Neopak™ XtraFlow™ Glass Prefillable Syringe are at the forefront of addressing challenges in subcutaneous drug delivery. The BD Effivax Glass Prefillable Syringe, for example, is designed for reliability and efficiency, particularly in high-volume vaccine production, addressing the need for scalable solutions in pandemic preparedness. The BD Neopak XtraFlow Glass Prefillable Syringe is designed to enhance patient comfort with reduced injection force. Coupling the BD Neopak XtraFlow Glass Prefillable Syringe and the BD SCF™ PremiumCoat® Plunger Stopper, BD can provide pharmaceutical companies with a system that is compatible with a range of biologics.

"These devices collectively address key challenges in the sector, including pa-

tient experience, device usability, and the scalability of drug delivery solutions," says Beth DiLauri, Director, Portfolio Marketing BD - Medical Pharmaceutical Systems.

The BD Neopak XtraFlow Glass Prefillable Syringe system was developed in response to pharmaceutical partners' needs for a device that could deliver highly viscous biologics without compromising patient comfort, explains Ms. DiLauri. The BD Neopak XtraFlow Glass Prefillable Syringe reduces the injection force required to deliver higher viscosity biologics, making it easier for patients to self-administer their medication. "This innovation not only addressed the specific challenge faced by our partner, but also can enhance the overall patient experience by minimizing discomfort during injection," she says. "Furthermore, BD's ability to scale up production and maintain high-quality standards ensured that the product meets the rigorous demands of both the pharmaceutical partner and regulatory bodies."

BD also recognizes the increasing importance of connectivity and wearable devices in enhancing patient care. The BD Libertas™ Wearable Injector is a ready-to-use drug delivery system that supports the shift towards self-administration by enabling the subcutaneous delivery of large volumes of medication, which is crucial for biologics.

BD also acquired Edwards Lifesciences' Critical Care to expand its smart connected care solutions. "This acquisition, along with the development of AI-driven clinical decision tools, positions BD as a leader in the integration of connectivity with drug delivery," Ms. DiLauri says. "We are committed to advancing our portfolio to include more wearable and connected devices that provide real-time data and improve patient outcomes."

Although specific product details cannot be disclosed now, BD is focused on developing future-ready solutions that integrate connectivity to support patients and healthcare providers in making informed decisions based on real-time data.

Credence MedSystems, Inc.: A Platform of Solutions Addressing Emerging Challenges

Ongoing trends in the pharmaceutical industry are creating significant challenges to the safe and effective delivery of injectable medications. And, there are several challenges that need to be solved by innovative drug delivery systems, says John Merhige, Chief Commercial Officer, Credence MedSystems, Inc.

For example, more difficult-to-administer formulations need to be delivered by more naïve users in less formal settings. In obesity and diabetes therapies, pipeline programs will require self-administration of formulations that require separation of constituents during storage due to stability or coformulation challenges. Dose volumes are getting both smaller (in applications such as ophthalmology and medical aesthetics) and larger (in biologics for chronic disease) while greater dose accuracy is needed due to safety issues. Users prefer a preattached needle to reduce the number of administration steps and facilitate administration, but formulations and suspensions with high concentration and viscosity are leading to injection failures stemming from needle clogging. And the general pressures on cost containment persist while enhanced sustainability continues to emerge as an industry imperative.

"Credence's philosophy of Innovation Without Change has resulted in a product portfolio that provides solutions to these challenges while reducing the risk and burden of implementation," he says. "Credence achieves this by utilizing industry-standard primary package components and increasing efficiency of existing manufacturing processes."

For example, the Credence Companion® provides integrated passive needle safety, numerous user cues to ensure safe

Credence Companion® and Dual Chamber offerings address challenges facing injectable drug delivery.

administration, and a reduced environmental footprint to promote adherence while supporting pharma's sustainability goals and eliminating steps in the manufacturing process. The Companion platform offers flexibility, enabling larger barrels to be employed as needed.

Additionally, the Credence Dual Chamber platform enables at-home administration of complex drug products that require separation of constituents during storage due to stability or co-formulation challenges. The Dual Chamber platform utilizes industry-standard prefilled syringes either with a pre-attached retracting needle or with a luer lock front end, offering flexibility to customize for different dose volumes, administration routes, and user requirements. "Whether point-of-care reconstitution or sequential injection of two liquids is required, the usability resembles that of a single-chamber PFS," says Mr. Merhige. "This has the potential to change the paradigm for these challenging formulations, allowing pharma manufacturers to reduce development expense and shorten time to market while presenting these medicines in formats that enable successful administration."

Companion and Dual Chamber are flexible enough to administer injectables as stand-alone systems or with an autoinjector. Credence is, therefore, collaborating with industry leaders on autoinjector offerings that can leverage the inherent benefits of both devices. The disposable single-use autoinjector is more common in the industry today. In this format, Companion's end-of-dose cues and integrated needle retraction simplify the autoinjector by removing functionality requirements it had previously needed to address. Beyond that, Companion helps to enable further adoption of a reusable autoinjector. After use, Companion protects the needle in the plunger rod, allowing for safe and easy removal by the user. And because Companion's integrated safety eliminates the traditional add-on wrap around device, the disposed portion represents minimal plastic in a small footprint, thereby accentuating the sustainability impact of the reusable autoinjector offering. "In this way, Companion with a reusable autoinjector creates the greatest sustainability value for the industry," says Mr. Merhige.

Crossject: Differentiating in Speed & Indications

When it comes to autoinjectors, patients prioritize devices that are easy to use, convenient to store, effective and safe in treatment, and affordable. The ongoing advancements in autoinjector technology offer significant benefits to various stakeholders by reducing the need for burdensome and expensive clinic and hospital visits. Consequently, the demand and acceptance of innovative autoinjectors are steadily increasing among patients, caregivers, advocacy groups, physicians, and cost-conscious insurance providers. Furthermore autoinjectors have a lower patient-to-patient and intra-patient dosing variability compared to oral or nasal routes of administration, thus ensuring the dose is accurately received, says Patrick Alexandre, Founder and CEO of Crossject.

Crossject's ZENEO® is a needle-free autoinjector platform designed to deliver a variety of drugs via intramuscular or subcutaneous injection. Its patient-friendly, compact design and simple administration make it especially well-suited for pre-hospital treatments and emergency situations. "The needle-free technology not only enhances patient experience, it also offers the potential to improve compliance and adherence, making it an attractive option for patients valuing ease of use and minimal discomfort," he says.

One the differentiating benefits of the ZENEO autoinjector is the speed of injection – it delivers the medication in less than 0.1 seconds. The rapid delivery effectively minimizes the risk of administration errors or needle lacerations, says Mr. Alexandre.

"Moreover, the high velocity of drug delivery utilizing ZENEO has shown promising drug delivery results, as highlighted in our latest clinical trial," he says. "The

Crossject's ZENEO® needle-free autoinjector platform.

study demonstrated that ZENEO achieves higher mean drug concentrations within the first 10 minutes as well as a quicker injection process, leading to a potential faster onset of action for the injected drug. This rapid response is crucial for conditions like seizures where it can prevent prolonged episodes and associated neurological complications."

ZENEO also has the potential to elevate the standard of care for a wide range of health conditions that require immediate, emergency treatment. The company's current focus is to provide patient-centric rescue solutions that are safe, reliable, and effective, with rapid drug delivery that can be easily administered when time is of the essence, such as the epilepsy market. Crossject is moving toward submitting a New Drug Application to the FDA in 2025 for Zepizure®. Additionally, Crossject is advancing two additional programs, ZENEO Hydrocortisone and ZENEO Adrenaline, with plans for market authorization filings soon after the Zepizure NDA submission.

ZENEO also holds promise for chronic conditions, says Mr. Alexandre. "Clinically, ZENEO has proven its capability to deliver both small and large molecules, regardless of viscosity, with the same precision and speed as our emergency drug applications. The ability to inject drugs easily and rapidly, without a needle and even through clothing, positions ZENEO as a differentiating factor in various therapeutic areas, including oncology, dermatology, obesity, cardiology, and respiratory care."

Duoject Medical Systems: Making Complex Lyo Therapies Accessible & Manageable

One of the main factors driving the injectable delivery sector is the development of biologics, including vaccines, antibody-drug conjugates, and monoclonal antibodies, which often cannot be delivered orally due to the complexity of their molecules and precise administration method requirements. Injectable therapies often provide rapid onset of action and improved bioavailability when compared to oral medications.

Duoject develops novel medical devices that enhance the safety, convenience, and compliance of injectable therapies, with a focus on patient-centric care. Its technologies aim to help reduce dosing errors and improve the patient experience by emphasizing ease of use and minimizing discomfort associated with injections, allowing patients to manage their conditions at home and reduce the need for frequent hospital visits.

Duoject's Raven is a new preassembled all-in-one reconstitution and injection device designed for seamless home care use. This device integrates both a diluent cartridge and lyo drug vial into a single, compact unit, enabling the reconstitution of the medication with a few simple steps prior to self-administration using a standard pen needle for convenience. Raven is a single-use, sterile device, eliminating the need to manually handle multiple components, simplifying the preparation process and reducing the risk of contamination and dosing errors, explains Daniel MacDonald, Director of Drug Delivery Systems, Duoject Medical Systems.

"This new design addresses a signifi-

Duoject's Raven reconstitution and injection device with preassembled containers.

cant challenge in the pharmaceutical industry: ensuring accurate and safe administration of reconstituted drugs in a home care setting," he says. "Traditional methods of drug reconstitution and injection often require multiple steps and a high level of precision, which can be daunting for patients, especially those with limited medical training. By simplifying the reconstitution and injection process into a single, user-friendly device, Duoject's Raven enhances patient adherence to treatment regimens, leading to better health outcomes."

Moreover, the device's safety features, such as hidden transfer needle, locking mechanism to prevent reuse, and consistent dosing improve the overall safety profile of injectable medications, addressing concerns of contamination and dosing inaccuracies, says Mr. MacDonald. "This innovation represents a significant step forward in making complex lyophilized injectable therapies more accessible and manageable for patients worldwide."

Enable: Hands-Free, Wearable Administration Delivers Up to 25mL

Biologics continue to dominate pipelines and portfolios. In fact, more than 45% of global biologics doses are greater than 5mL. These products are viscous, concentrated, and are increasingly required to be high-volume to be efficacious. Large volumes of medication often require administration either intravenously or subcutaneously using a syringe and needle, or via a syringe pump – delivery methods that can involve lengthy clinic visits, large needles, and often painful procedures. This is where Enable sees a clear need for innovation.

The Enable enFuse is a first-in-class wearable technology, which has been developed through dozens of human factors studies to ensure the best product for patients.

"The main obstacle with autoinjectors is they often don't have the capacity to support large volumes of medication," says Matt Huddleston, Chief Commercial Officer, Enable. "This is why we believe enFuse offers such a unique and incredible opportunity. enFuse features the first-ever hands-free, wearable technology designed to deliver large volumes of therapeutics subcutaneously (up to 25mL with a single enFuse, or up to 100mL with multiple enFuses worn simultaneously), in which patients receive their needed treatment through a simple injection under the skin, instead of intravenously."

Purposely designed to be completely mechanical, enFuse doesn't require wiring or tubing, therefore allowing hands-free administration that enables patients to move freely and perform light to moderate activities while medication is being administered. After adhering to skin with adhesive, a thin, hidden needle comfortably and silently delivers medication into the skin. An indicator shows when the medication has been fully delivered and the needle automatically retracts.

With a design that allows compatibility with small molecule and biologic drug formulations across a range of viscosities and volumes, enFuse is applicable across various therapeutic areas and offers pharmaceutical partners a unique opportunity to differentiate their drug development programs and medication offerings. Pharma companies also have greater flexibility for streamlining formulation changes from intravenous to subcutaneous with enFuse technology flexibility, potentially increasing time to market, he says.

In October 2023, the FDA approved the first enFuse combination product – the EMPAVELI Injector – marketed by Apellis, to enhance self-administration of EMPAVELI for adults with paroxysmal nocturnal hemoglobinuria (PNH). As a result, the EMPAVELI Injector has elevated the standard of care in PNH and the treatment experience for patients living with this chronic condition, says Mr. Huddleston. Most recently, Enable announced a partnership with Serina Therapeutics to develop and commercialize SER-252, an investigational apomorphine therapy, in combination with enFuse for a potential best-in-class treatment of Parkinson's disease.

He explains that unlike other apomorphine treatments that require daily, time-consuming infusions via an electronic pump – leading to patient and physician

burden and potential significant skin reactions – enFuse allows patients to self-administer SER-252 with a quick, simple injection under the skin, all from the comfort of their home.

In addition to Apellis and Serina, Enable has entered into multiple shared-value partnerships with other leading drug developers, including CSL Behring, Roche, Sanofi, UCB, and Viridian.

Flex's smart syringe reference design platform improves therapy adherence monitoring and accelerates time to market.

Flex: Smart Syringe Design Platform Accelerates Time to Market

Exceptional user-centered design and human machine interface are the foundation of rapid adoption of autoinjectors by leveraging natural behaviors to make complex devices seem effortless. Innovations driven by technology advancements in connected devices – such as artificial intelligence for decision support – enhance safety and accuracy through real-time monitoring and predictive analytics, and can further fuel customer confidence and increase adoption.

Last year, Flex introduced a reference design platform for developing prefilled syringes (PFS). "The smart syringe reference design platform is part of our goal to enable pharma companies to offer the most advanced drug delivery solutions for patient care," explains Jennifer Samproni, Chief Technology Officer, Health Solutions, Flex. "It provides advanced technology housed in a common syringe form factor for ease of use and improved dose accuracy, and its sensors for connectivity allow data collection and post-use analysis as well as the ability to monitor patients remotely."

These new features were designed to fit into small, volume-fill syringes, such as a 1mL PFS. Because the syringe's piston incorporates digital features and transfers data through Bluetooth low energy (BLE), the drug can be administered and easily monitored without compromising patient privacy and cybersecurity, she says. The smart syringe accurately senses the delivered dose and transmits the injection log together with a timestamp to a clinical study portal. This allows effective injection tracking, while enabling post-use data analysis to enhance the efficacy of clinical trials.

"We also designed the smart syringe with sustainability in mind by using eco-sustainable resin material to lower the product's carbon footprint and by ensuring the syringe is easily disassembled at the product's end-of-life to enable circular economy processes," says Ms. Samproni. Cybersecurity concerns have been addressed with the industry-standard AES128-EAX scheme, which provides encryption to protect transmitted dose data, as well as syringe-to-cloud secure authentication.

Flex's smart autoinjector reference platform was designed to enable pharmaceutical companies to accelerate time to market, reduce costs, and boost reliability while ensuring patient compliance and minimizing environmental footprint. The platform was recently used in a product optimization assessment carried out by a leading pharma company. The study helped highlight the varied experiences that patients have with different injection devices and demonstrated the value that reusable autoinjectors with connected features deliver to patients.

The research involved a focus group of patients from Europe and the US, most of whom had no prior experience using connected devices; they were simply shown key features of Flex's reference design platform and provided feedback. "The results helped our pharma customer address new device development based on real patient needs, preferences, and concerns," she says. "Involving a prototype like the smart autoinjector helped them mitigate the risks of designing and testing something from scratch."

Kahle Automation: Assembling Device Components Without Risking Damage

A rapidly expanding market today is a class of Type 2 diabetes drugs that not only improves blood sugar control, but may also lead to weight loss. These

Kahle Automation loading finished pen injectors into trays after assembly.

glucagon-like peptide 1 (GLP-1) agonists are most commonly administered via injection given daily or weekly. Autoinjectors and pen injectors play a key role in allowing the patient to perform this as a self-injection at home. Not surprisingly, drug/device manufacturers are desperately trying to increase their production capacity to capitalize on this market growth, says John Wuschner, President, Kahle Automation. Some aspects of this expansion are straightforward (make more drug) by processing or storing more, but on the device/packaging side, assembling dozens of precision components using higher output systems requires crossing boundaries that have been avoided in the past based on perceived risk and/or capital constraints.

"Market growth is addressing the capital constraint issue, but these devices utilize components with unique features requiring complex assembly and feeding systems, and getting these designs from current to higher volume production rates to meet the surge in demand requires an automation partner who not only understands how to get thousands of components per minute to the assembly machine, but also in a controlled manner without functional or cosmetic damage," he says.

Feeding of components without causing damage is critical when one considers that an autoinjector or pen injector could have 10 or more different components needing to arrive at the machine at rates exceeding 400 per minute. Mr. Wuschner says: "There are control features on every component that can affect dosage, functionality or even safety, and proper handling must be ensured to guarantee that these features are preserved. The feeding system designer needs to take each component's purpose into consideration during the development stage and work in partnership with the device manufacturer to arrive at a low-risk solution that meets the production requirements. Sometimes this means that slowing the feedrate itself while multiplying the tooling will allow for this needed control."

This is also true of the assembly processes. In order to guarantee high yields at higher outputs, faster is not always better. Running a slower speed scalable through multiplying the tooling allows for a more efficient and controlled assembly process. It also allows more time for processes (e.g., welding, sealing, threading) instead of working on the edge of the process, he says. This improves consistency and mitigates the risks of assembly because there is a bigger window of operating parameters available.

"By so doing, not only is the probability of rejects reduced, but also the key performance indicators of the product can be managed to generate results that perform equivalently lot to lot, and inspections can be more robust in a stable environment." A side benefit to this theory of operation is that the equipment is operating at a more controlled rate with lower vibration and wear and generating higher productivity (reduced downtime and maintenance costs).

Lifecore Biomedical: Data-Driven Decisions for Injection Delivery Options

Compared to vials and syringes, getting an autoinjector to market may take more time, money, and resources, which could potentially delay the commercialization of an important product. Some companies may choose this route, while others may decide to commercialize in a vial and then do work to bring an autoinjector to market post-commercialization. Finding a CDMO that can support scale-up and support flexible container configurations in either situation is valuable.

To mitigate challenges during combination product design verification process and to help de-risk future activities, it is important to make data-driven decisions, says Julie D'Ascenzo, New Business Devel-

Lifecore Biomedical offers expertise to support drug lifecycle management.

opment Director at Lifecore Biomedical. "This can be done by performing feasibility or characterization studies that allow you to evaluate the component and system-level performance," she says. "By performing early-stage feasibility work, you will gain confidence that you have selected the appropriate primary packaging or device for your molecule."

Of what should early-stage feasibility work consist? First, it is important to conduct a study that spans its shelf life so you understand what can happen 2-3 years down the road. Performing testing at T0 and accelerated aging will give you a full picture of what your product looks like over its shelf life in a shorter period. Second, it is important to understand some of the challenges that can occur between your drug and container, in this instance a PFS. Areas of concern may be dewetting, particulate formation, and mechanical performance alteration. To ensure that there is no alteration of the mechanical performance of your device over its shelf life, performing breakloose glide force and injection time testing in combination with a lubrication layer analysis at T0 and accelerated aging are studies that allow you to make data-driven device selection decisions.

Another aspect to consider is if you are transitioning from a prefilled syringe (PFS) to an autoinjector. Proactively obtaining dimensional data of a PFS and sharing it with your autoinjector manufacturer up front can help decrease overall timelines, says Ms. D'Ascenzo. "While drawings from PFS manufacturers are useful, being able to go one step further to understand all the potential sources of dimensional variability in the system that make up your autoinjector gives insight into what dimensions are critical to device functionality," she says. "Performing a dimensional evaluation will give you more detailed information and allow you to understand from where potential variation is coming. By conducting this work, you are understanding your full system earlier on and better positioning your team for success."

Nemera: Pen Injectors Facilitate Multi-Dose, High-Volume Dosing

Autoinjectors are quickly becoming the most popular type of self-injection device primarily because they are very intuitive and simple to use. Their design is user-friendly, often requiring just a single press of a button to administer the medication, which minimizes the risk of user error and ensures accurate dosing. However, it is important to note that autoinjectors are typically not designed for multiple uses, which raises concerns about sustainability, says Cécile Gross, Global Category Manager, Parenteral, Nemera. Despite this, their user-friendly utilization continues to drive their popularity in the market. Nemera's PenDURA and PenVARIO platforms facilitate multi-dose pen injector ranges.

"Our pen injector range, including PenDURA and PenVARIO, addresses the challenge of diabetes by offering practical benefits and sustainable options for patients with chronic diseases," she says. "Multiple-use capability is practical for patients who need to inject themselves several times a day. Making treatment easier to take and reducing waste compared with single-use devices provides a cost-effective long-term solution."

Nemera recently collaborated with a generic drug manufacturer to address the "diabesity" market with a sustainable and economical solution. "They needed a cost-effective option for the Rest of the World (ROW) markets and our custom PenDURA AD was the answer," says Ms. Gross. "Designed for GLP-1 injections, it is reusable, which offers a very low cost per injection and maintains sustainability. Working together, we have succeeded in providing a solution to our customers' needs."

Nemera is also addressing the challenges of biologics, self-administration, and sustainability in a single device with its Symbioze™ reusable on-body injector. Sumbioze is designed for continuous medication delivery, enhancing patient comfort and compliance for those managing chronic conditions.

The Symbioze drug delivery system is

a connected and reusable on-body injector suitable for large-volume injections. With embedded Bluetooth connectivity, a recognition system between the reusable and the disposable part, and a dedicated patient application, Symbioze allows patients to monitor their treatment progress in real-time, receive reminders for upcoming doses, and track injection history – all from a smartphone or tablet.

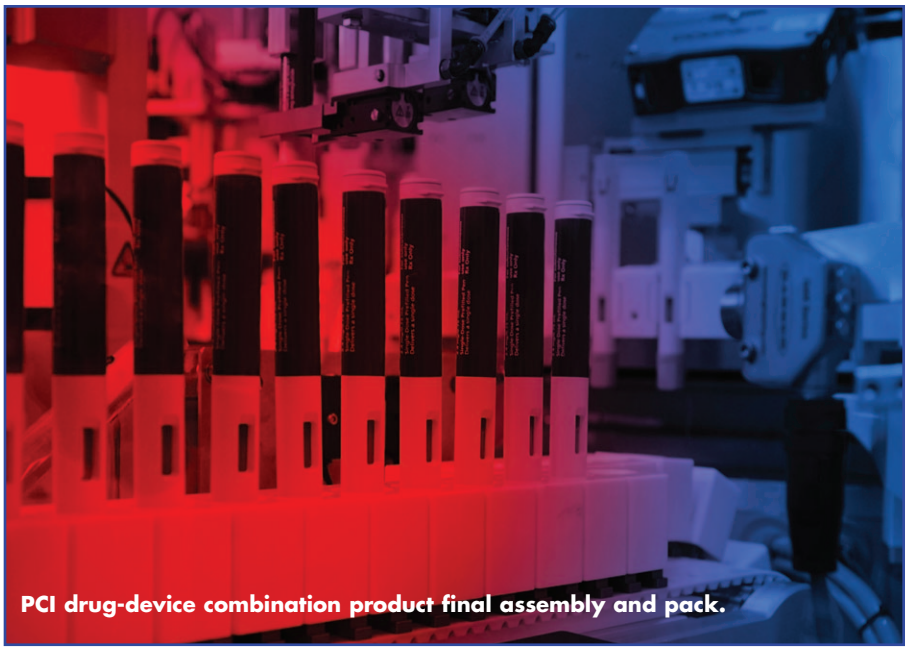
"Connectivity and wearable devices are transforming the way patients manage their health, and we are working on this path of innovation," she says. "By combining advanced wearable technology with connectivity applications, we are enhancing patient engagement, improving treatment adherence, and leading to better patient health outcomes."

Nemera is currently pursuing new markets focusing on high-dose and high-volume medications. Symbioze and Safe'n'Sound® facilitate the administration of high-dose biologics to make treatments more accessible and effective for patients, she says.

PCI Pharma Services: Comprehensive Clinical to Commercial Injectable Delivery

Biopharmaceutical companies are actively incorporating autoinjector drug delivery technology into their product portfolios, recognizing the competitive advantage these devices offer in terms of differentiation and patient satisfaction. As a result, the autoinjector market is witnessing a surge in innovation, with companies investing to enhance device features and compatibility with a diverse range of biologic drug products.

Indeed, the growth in injectables is driven by biologics – which in most cases



PCI drug-device combination product final assembly and pack.

today cannot be effectively delivered orally – and the desired delivery is self-administration. Spanning the cycle from development to commercialization, PCI offers comprehensive, scalable injectable drug delivery solutions for large and small molecule life-changing therapies. "Our integrated sterile drug manufacturing and injectable final assembly and packaging solutions support biopharma companies in optimizing dosing, and provide convenient, easy-to-use, patient-centric therapies to patients," says Bill Welch, Executive Director Market Development, Advanced Drug Delivery, PCI Pharma Services. "Our consultative methodology and extensive experience enable a flexible and agile approach for our clients, ensuring the right solution for the patient to realize improved health outcomes around the world."

Driven by innovation and patient-centricity, PCI's design and development expertise, combined with device assembly and drug delivery packaging capabilities, offer flexible solutions for a diverse portfolio of conventional and specialty injectable drug-device combination products. PCI enables rapid growth of the drug-device combination product for both the sterile fill-finish (SFF) and the final assembly, packaging, and labeling of the drug-device combination.

He says: "Clients are thinking about their drug-device strategy earlier in the development process, with many biopharmaceutical companies investing in research and development to not only enhance device features and compatibility with a diverse range of large and small molecule drug products, but also introducing and evaluating them as viable dosage forms earlier in clinical trials through parallel development strategies."

Meeting the exponential growth in the development and use of autoinjectors, PCI continues to invest in device-agnostic, innovative, scalable, injectable combination product final assembly, packaging, and labeling technologies for autoinjectors, prefilled syringes, PFS with needle safety device, pens, and on-body injector (OBIs).

"Wearable OBIs are currently a small segment of the market when compared to pens, PFS, and autoinjectors, and can be generally divided between those that are "prefilled and preassembled" and those that require filling and/or insertion of the drug container at point of use," Mr. Welch

explains. Similar to autoinjectors, there is an emphasis on simplicity for the patient, as exemplified by the "peel, stick, and click" approach for prefilled and pre-assembled OBI. As a device-agnostics service provider, PCI offers final assembly or kitting, packaging, and labeling services for OBI, as well as SFF of the containers used in OBI.

"We have the scalability to handle the dynamic volumes of biopharmaceutical therapies, whether large or small, from early-phase clinical trials through to commercial supply of niche personalized medicines to large, annual volume treatments," says Mr. Welch.

Phillips Medisize: Pen Injector Appeals to a Range of Customers

The injection market is currently dominated by pen injectors for insulin delivery, but autoinjectors are becoming more common and in a broader range of indications. Each device type has pros and cons. Pen injectors allow the patient to adjust the delivered dose, critical for drugs such as insulin-requiring titration. Also, pen injectors enable multiple injections from the same drug container, reducing the cost per dose. However, they are considered more complex to use than autoinjectors. The rapidly evolving injectable GLP-1 market will impact the uptake of new devices, with single-use autoinjectors currently gaining popularity for their convenience. Sustainability considerations will likely drive the market towards multidose disposable pen injectors. Additionally, take-back schemes are being explored to reduce waste, but in the longer term, continued focus on reducing waste will likely increase interest in reusable devices, explains Iain Simpson, Director of Business Development at Phillips Medisize.

The Envoi Pen from Phillips Medisize is patient-friendly, minimizes misuse, and delivers high-concentration drugs.

Most of the pen injectors in the market have been developed by pharma companies for specific drugs. "Phillips Medisize spotted an emerging need for a pen injector with a familiar look and feel to existing pen injectors that could offer a platform to a wide range of customers," he says. "In developing this solution, which we call Envoi, we also incorporated some new benefits into the design, such as shorter button travel, which makes it particularly suited to delivering larger doses and for patients with smaller hands."

Envoi is a platform solution that offers a range of models suited to deliver a range of therapies, including insulin, GLP-1s, and hormone replacement. Henrick Leisner, Envoi Platform Manager at Phillips Medisize, says: The Envoi Pen has been designed to be patient-friendly, minimizing the risk of device failure due to misuse, and is suitable for delivering a range of drugs, including high-concentration drugs. "Furthermore, it has been designed for highly automated, high-volume manufacture, enabling reliable and economically viable supply to the largest drug markets on a global basis," he adds.

Phillips Medisize is also a leader in developing connected devices that accurately measure medication use, allowing a digital health intervention to be adapted in real-time to changing patterns of medication use. Dr. Simpson explains: "Working with Bayer, we brought the first drug-device combination with a regulated companion digital service to market. Medication non-adherence is a big issue for the industry, resulting in lost pharma company revenue

as well as higher medical costs and lower economic productivity. Non-adherence is a complex behavioral issue requiring personalized and dynamic interventions, that is, adaptive to any patient's current circumstances. We are working with behavioral experts to develop connected health solutions that address this need."

Portal: Fast & Easy Delivery of High-Viscous Biologics

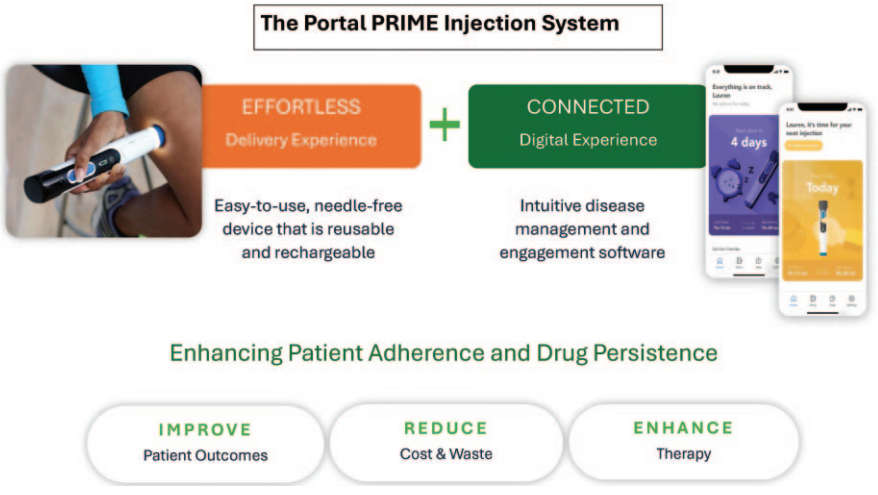
Empowering patients to manage their own care at home can lighten provider workloads, reduce demand for expensive clinical services, and make adherence more convenient for patients. The Portal PRIME device is an easy-to-use, needle-free, reusable injector that digitally controls the administration of high-viscosity biologics and monoclonal antibody treatments.

"Typical biologic concentrations are ≤200mg/mL; with increased dose needs, there becomes a trade-off between concentration, which leads to higher drug volume or to higher viscosity," explains Christina Mastandrea, Vice President, Clinical Research, Portal. "New drug delivery systems are needed to handle high-viscosity drugs or higher volumes in a patient-acceptable format."

Portal's PRIME device can deliver volumes up to 2.0mL at high viscosities (up to 1,200cP) in 0.6 seconds. It can be connected to patient apps or the wellness team to provide a more complete data picture. PRIME is well-suited for patients with a chronic disease who need to take subcutaneous injections on a regular basis.

Portal is expanding its portfolio to include a needle-based Smart Syringe that retrofits standard 1mL or 2mL prefilled syringes (PFS). "Similar to PRIME, this technology leverages a high-powered linear actuator, sophisticated real-time control algorithms, and cloud connectivity that also offers a transformed and safer user experience," she says.

Ms. Mastandrea continues: "Connectivity and wearable devices must be designed with end users in mind. Clinicians are interested in easy access to relevant clinical data, efficient integration of the digital platform into the clinical workflow, and ultimately improved treatment outcomes. For patients, the application's usability and design are important for initial adoption, as are the potential for fewer clinical visits and thus fewer co-payments along with reduced time invested in appointments and travel to clinics. Portal continues to improve its connectivity platform to ensure a seamless and informative experience for both clinician and patient, and the platform meets the highest quality standards."



Portal's PRIME reusable injector digitally controls administration of highly viscous biologics.

Sanner Group: Supporting Drug Delivery System Development

The injectable drug delivery sector is pouring huge resources into expanding capacity for GLP-1s. These drugs were developed originally to treat Type-2 diabetes, but have proven effective in treating obesity and, more recently have been shown to offer some protection against cardiovascular disease. While most GLP-1 drugs are injected, oral GLP-1s, such as Rybelsus (semaglutide), are being developed. However, sales of injected GLP-1s should continue increasing for some time due to relatively infrequent injections and patient-centric injector designs.

Another trend is large-volume injections. Multiple drugs have been or are being reformulated from intravenous infusion to subcutaneous injection. These therapies tend to require high-volume or high-viscosity injections, which has prompted the development of large-volume autoinjector platforms and onbody delivery systems. The majority of "traditional" autoinjector platforms are based on a 1mL staked needle. More recently, 2.25mL syringes have been supported and the increasing capability for larger volumes has been extended to 3mL in cartridge-based autoinjectors.

A third trend is increasing innovation

An autoinjector design from Springboard Pro, a Sanner company.

in ophthalmic injections. These have specific development challenges because they have very low particulate limits, they must not draw fluid back up the needle, they must not increase intraocular pressure, they have small dose volumes and precise dose accuracy, and they must be targeted very accurately.

Autoinjectors offer increased usability over vial-and-syringe or prefilled syringe presentations. Vials require multiple user steps to transfer the drug into a syringe and then inject into the patient. "In many cases, the drug is lyophilized so the user has to reconstitute the drug, too," says Tom Oakley, Vice President of Design & Development, Sanner Group. "These additional steps increase the risk of error and loss of sterility."

He continues: "Prefilled syringes reduce the number of user steps compared to vials, but they can be difficult to use, especially if the drug has a high viscosity and/or high volume, of if the user has issues such as hand tremors, arthritis, or impaired visibility. In addition, unless they have a needlestick protection system, the user risks needlestick injuries from prefilled syringes."

Sanner supports companies in the development of drug delivery systems, taking them from initial requirements through design and development, verification and validation, and into scale-up and production. "Within that process, safety, functionality and design are equally important," says Mr. Oakley.

One example is an ergonomically shaped "flange" (finger rest enlargement) for a prefilled syringe. This improved flange increases safety and ease of use due to its ergonomic shape and non-slip surfaces. These features are especially important where injection accuracy is critical, such as ocular injections and in cosmetic procedures. He says: "Sanner's optimized manufacturing process ensures that the flange achieves the smallest shot weights possible with two-shot molding."

SCHOTT Pharma: Prefillable Polymer Syringe Simplifies Subcutaneous Infusion

Autoinjectors ensure consistent and reliable dose delivery. This is particularly important for the efficacy of treatments, especially in the case of chronic conditions. SCHOTT Pharma's prefillable polymer syringe is designed to ensure precision and quality in dosing. This is particularly crucial for biologic medications. Additionally, polymer syringe maintains the stability of the drug, ensuring its efficacy until it is administered.

The polymer syringe also features a user-friendly design, reducing the risk of administration errors. "This not only enhances the overall user experience, but also contributes to patient safety," says Nina Krautwurst, Global Product Manager Polymer Solutions at SCHOTT Pharma.

Furthermore, the polymer syringe can be customized to accommodate various viscosities and volumes, making it versatile for different types of medications and devices. She says: "This flexibility allows healthcare professionals to choose the most suitable option for their specific needs, ensuring optimal drug delivery."

In line with the growing demand for eco-conscious medical devices, SCHOTT Pharma uses sustainable materials to minimize the environmental impact of

Polymer syringes in production at SCHOTT Pharma.

its prefillable polymer syringe SCHOTT TOPPAC®. Additionally, SCHOTT TOPPAC can store drugs down to -100°C and is successfully used in combination with highly sensitive drugs such as mRNA.

"With SCHOTT TOPPAC, we ensure that people around the world can administer their medications safely and easily," says Ms. Krautwurst.

By combining KORU Medical's expertise in pump systems with SCHOTT's expertise in prefillable polymer syringes for large volumes, SCHOTT can help improve the market introduction of infusion therapies while simplifying the subcutaneous infusion of large quantities of medication. For example, one pharmaceutical client was developing a new biologic therapy that required precise, subcutaneous administration, she explains. They faced challenges with patient compliance and dosing accuracy using traditional syringes.

"The ergonomic and easy-to-use design of our prefillable polymer syringe makes self-administration straightforward with the KORU system, resulting in higher patient adherence," she says. "Also, the precision engineering of our syringe ensured consistent dosing, which is critical for the efficacy of biologic treatments. Lastly, patients reported a more positive experience due to reduced injection anxiety and ease of use, leading to better overall treatment outcomes."

SCHOTT Pharma recently launched the cartriQ® platform of pre-washed, sterilized, and siliconized ready-to-use (RTU) cartridges, covering all relevant formats, from 1.5mL to 20mL, to safely inject crucial therapies at home. "As a RTU product, pharmaceutical companies can always expect the same quality and have higher flexibility in production to actual market demand, ensuring a consistent supply of critical drug products," says Robert Lindner, Global Product Manager Bulk & Sterile Cartridges at SCHOTT Pharma.

Most recently was the launch of 10mL cartriQ cartridges, which are suited for sensitive biologics. The containers are compatible with Ypsomed's Ypsodose, making the fully assembled system the first on the market that is prefilled and preloaded, significantly reducing the handling steps for end-users, says Mr. Lindner.

Singota Solutions: Aseptic Manufacturing Tailored to Client Needs

There are several factors driving growth in the injectable delivery business sector. Many of today's common diseases require injection of the therapeutic to avoid complications of the effects of the digestion system on the drug's therapeutic effects. New infectious diseases such as COVID-19 will require injectable vaccines.

Autoinjector technology offers many advantages. Self-injection via autoinjectors allows for improved dose accuracy and reduced cost of administration. Design features provide benefits such as prevention of accidental activation, reduced needle stick accidents, and visual or audible indicators of dosage success. Autoinjectors are now being designed with mobile app connectivity that keeps track of dosing frequency and even providing reminders to patients to take their medication.

CDMOs can play an important part in the development of an autoinjector/therapeutic product. The formulation and fill-finish processes need to be compatible with the design of the autoinjector. Material compatibility, container closure integrity, and product stability considerations are all necessary in moving a product through the development phases.

Singota Solutions is a CDMO dedicated to overcoming obstacles in the drug development pipeline. "Specializing in small-batch aseptic filling, aseptic manufacturing solutions, and injectable formulation development, Singota offers comprehensive services designed to expedite the progression of clients' products toward clinical trials," says Will Powers, Senior Director of Business Development & Marketing for Singota Solutions. "Our GMP-compliant warehousing and 3PL op-

erations ensure the integrity and safety of pharmaceutical products, including those requiring cold-chain pharmaceutical storage."

Stevanato Group: Single-Use Autoinjector Features Versatile Design

A number of biologic therapies are now coming off patent so biosimilar companies are seeking platform products that offer low up-front cost and fast time to market. Novel therapies moving from healthcare settings to the home, meanwhile, are accelerating the move towards self-administration and therefore increasing the demand for simple and proven injectable delivery systems to enable safe and effective self-administration. Whether managing a chronic condition or dealing urgently with a life-threatening allergic reaction, patients are playing an increasingly central role in their own medical care through the self-administration of essential drugs.

"Autoinjectors are proving popular because of their simplicity and ease of use which enables them to self-administer their therapies," says Josh Gordon, Product Manager for Drug Delivery Systems at Stevanato Group. "And, they are becoming more popular with pharma and biotech companies because of their optimal delivery solution that presents a proven user interface and efficacy balanced with a favorable cost of ownership."

While maintaining the historically proven user interface of a 2-step autoinjector for the patient, Aidaptus® is a single-use autoinjector with a versatile design that accommodates both 1mL and 2.25mL prefilled glass syringes in the same device form factor and, with no change parts, accommodates flexible fill volumes in the prefilled syringe, he explains. "These unique product features provide value to the pharma customer by offering class-leading flexibility and adaptability in the development and manufacturing of combination products. This is demonstrated when combination products have multiple dose volumes. Aidaptus allows the pharma to test a single device design in development and minimize final assembly recipes to execute in manufacturing and SKUs to commercialize."

In addition to the value the product brings, the Aidaptus commercialization is supported by Owen Mumford and Stevanato Group's joint collaboration that amplifies Aidaptus' value to the pharma by bringing the full complementary capabilities of the two organizations to bear, Mr. Gordon says. "Leveraging Owen Mumford's pioneering autoinjector experience and expertise along with Stevanato Group's integrated device capabilities, including primary container, device, manufacturing, assembly equipment, and analytical services, provides a scalable and continuity of supply offering to the pharma industry. Supported by the Owen Mumford and Stevanato Group's collaboration, the Aidaptus offers unique value and opportunity to support speed to market and consolidation in scaling and marketing combination products."

Terumo Pharmaceutical Solutions: Packaging for Compatibility

There are more than 3,000 injectable drugs in the pipeline – many of which are sensitive biological drugs with potential stability challenges. Thus, primary packaging solutions must reduce drug-container interactions throughout the shelf life. In addition, many biologic drugs in the pipeline are targeted towards smaller patient populations, which requires the manufacture of smaller batches even in prefilled syringes (PFS) – without compromising on quality. Flexible filling lines in combination with ready-to-fill components like PLAJEX™ is the answer to address this trend, says Thomas Isaac, Global Product Manager, Terumo Pharmaceutical Solutions Division. Terumo works with external partners to ensure compatibility of PLAJEX with autoinjectors and safety devices for an integrated solution.

PLAJEX™ 2.25mL with tapered needle for biotech formulation (Terumo Pharmaceutical Solutions).

Terumo also supports its partners at both the development and commercial phases. In one case, Terumo helped introduce a biosimilar product in an autoinjector. "By integrating the manufacturing of

primary containers with essential features for the biotech market, such as silicone oil-free barrels, along with a comprehensive range of services – including fill-finish, assembly with an autoinjector, and regulatory support – Terumo simplified the traditionally complex supply chain involving multiple players," he explains. "This allowed the pharmaceutical company to focus on drug substance preparation. As a result, the biosimilar product in the autoinjector has been registered in Europe, the US, Japan, and many other countries."

Providing the most suitable injection needle for a specific drug constitution, route of administration, and injection site can be paramount for treatment compliance and patient adherence. To ensure the immediate availability of all necessary elements for an uncompromised procedure, it is beneficial to co-pack the selected needle with a treatment kit. To streamline automated co-packing, Terumo has developed a comprehensive range of needles provided in primary packaging featuring an ergonomically shaped cap-case receptacle – the K-Pack™ range. These needles are designed to occupy minimal space and have round shapes for enhanced pick-and-place efficiency. They also feature color-coded, tamper-evident labels with 2D-barcode capabilities, accommodating all major automation technologies. Additionally, the implementation of a full 360° camera inspection is essential for optimal packaging processes, facilitating device identification and inventory control.

Terumo has also developed hypodermic injection needles that meet the demands of long-acting drug placement. "Leveraging advanced cannula design and manufacturing capabilities, Terumo has marketed needles that enable the injection of larger medication volumes into the gluteal area," says Mr. Isaac. "These needles, which feature lengths around 51mm and thin-wall technology, are designed to enhance user and patient comfort through reasonable flow rates."

Vetter: Thoughtful Consideration of Autoinjector Development

As chronic diseases rise, there is a related spike in biologic approvals. This results in a co-existence of blockbuster products and small-batch drugs developed depending on the demand of the patient group. Many of these diseases require regular injections and experience significant increase in demand.

In this context, patient centricity is becoming a greater priority as many look for homecare solutions that allow for self-administration. This shift from intravenous (IV) administration to subcutaneous (SC) is prompting pharma and biotech customers to outsource based on the unique requirements and lifecycles of their molecules.

Autoinjectors are rising in popularity, largely due to their intuitive functionality and ease of use, even for patients with limited dexterity. As a result, it is much more likely for patients to adhere to their directed doses, which improves overall care. These devices have no readily visible needle and use "push on skin" technology that often reduces patient anxiety. Unlike an injector pen, autoinjectors include needlestick prevention as an added safety feature. As a form of prefilled syringe, autoinjectors include a single dose that minimizes the risk of incorrect dosing, even for patients with little training. With controlled injection time and speed, patients experience less pain.

"There are multifaceted challenges in the injectable sector that we strive to address," says Carolin Gruber, Product and Service Manager Primary Packaging and Devices, Vetter. "Large-volume injections, for example, are growing in popularity due to new molecules (e.g. mAbs) with high concentrations and a rise in homecare. As the industry shifts from IV to SC formulations, we are evaluating devices with volumes that exceed 2-3mL and new wearables that support patient self-administration."

Sustainability is also a challenge. As a high-consumption industry with high plastic production, Vetter is focusing on making smart and environmentally conscious decisions as a responsible member of the value chain. This includes providing all-paper packaging solutions and discussing the implementation of recycling streams without jeopardizing quality.

Finally, Vetter is working to include flexible manufacturing concepts to account for small batch sizes for rare diseases and personalized medicines, and the corresponding frequent changeovers required, says Ms. Gruber.

"As a full-service provider, long-term thinking is essential to get ahead of customer needs and serve as an experienced and strategic manufacturing partner," she says. "Launching an autoinjector is a strategically, technically, and operationally complex process that requires thoughtful consideration every step of the way."

West: ODBS Evolves to Improve the Patient Experience

Injectable drugs are the fastest growing drug segment and the rise in biologic drugs requires innovation in drug delivery methods due to their complex molecular structure. Regulations continue to evolve with review times increasingly expedited,

West's SmartDose® 3.5 On-Body Delivery System and SmartDose®10 On-Body Delivery System.

with approximately 76% of drugs getting approved on their first cycle in 2022. Additionally, there is a race between drugs targeting the same indication or therapeutic area, particularly in biosimilars, with CDER approving more than 53 biosimilars referencing 17 innovator biologics; 42 are currently on the market.

Chronic conditions require long-term therapy, which has facilitated innovation and increased advancements and improvements in the patient experience. As therapies become more complex and shift towards self-administration, pharma companies are under pressure to bring novel devices to market that are intuitive and easy to use for patients. "It's not only a matter of preference – regulators are listening," says Shari Krusniak, Director, Marketing Strategy, West Pharmaceutical Services. "They've started capturing the experiences, perspectives, needs, and priorities of patients as part of the FDA's Patient-Focused Drug evaluation. Their goal is to give patients more of a say in drug development and evaluation."

Device development is a complex process, and the delivery technology can hinder patient experience. "Knowing our customers face these challenges, we aim to support their development with services and solutions that drive better patient outcomes," says Ms. Krusniak.

West developed the SmartDose® portfolio of on-body delivery system (OBDS) devices to offer patients with chronic health conditions, who require medication injections, a reliable, convenient, and easy-to-use method for home-based drug administration. SmartDose is available in both 3.5mL and 10mL, consists of a battery-powered, wearable on-body injector with a separate, prefillable, polymer-based cartridge that is filled with the drug product. "The OBDS incorporates human factors and usability testing to deliver a truly patient-centric approach to self-administration," says Gurmeet Singh, Senior Director, Business Development, West Pharmaceutical Services.

SmartDose OBDS was the first large-volume wearable to be approved as a combination product by the FDA, this technology has since evolved with multiple generations, with the goal of improving adherence and patient experience across a range of dose volumes, explains Ms. Singh. The SmartDose 3.5mL and 10mL devices are now used with two separate globally approved therapies in the market.

Disclaimer: West's SmartDose® on-body injector platform is not independently cleared or approved by any regulatory body for general healthcare professional or patient use, nor is it available for general commercial purchase. Its distribution and use are subject to applicable regulatory requirements for clinical investigation, and for marketing authorization, as used in combination with a specific drug or biological product. Compatibility with any particular drug or biologic must be confirmed, and its ability to achieve the desired patient benefits must also be confirmed, on a case-by-case basis. Important product and safety information and warnings available on West's website.

Ypsomed: A Range of Injectors for a Range of Indications

There is huge demand for pens and autoinjectors to support the market growth for once-weekly GLP-1 injections for treating Type 2 diabetes and obesity (diabesity). The latest GLP-1 type drugs can be formulated for multidose injections from a pen or as a single injection from an autoinjector. Ypsomed is positioned to provide both devices, depending on the marketing strategy of the pharma customer.

"Some of the early once-weekly therapies for GLP-1s for treating diabesity were based on an antibody fragment that was only available in an autoinjector," explains Ian Thompson, Vice President Account & Business Development, Ypsomed. "Newer once weekly GLP-1 drugs are simpler pep-

The complete range of Ypsomed injectors.

tides that can be formulated and administered using a multidose pen injector. For a one-year therapy, a patient needs only 13 pens containing 4 weekly injections compared to 52 single-use autoinjectors. In this case, the pen injector option is more sustainable, and we expect demand for pens to increase over time for GLP-1 therapies."

Other key growth drivers include the number of new antibody and oligonucleotide therapies for treating autoimmune diseases, rare diseases, and new therapy areas such as neurology diseases and immuno-oncology drugs. Demand is increasing for larger volume injections of high antibody payloads, which has led to the development of new platforms that deliver up to 5mL handheld injections, such as the YpsoMate 5.5 and 5-10mL patch injections like YpsoDose.

Connected solutions are also pivotal. Ypsomed Digital Health provides pharmaceutical companies with fully integrated digital solutions combining injection devices with comprehensive digital patient tools. "Our connected devices deliver support for patients throughout the injection process and capture accurate and unbiased real-world data," says Mr. Thompson. Key connected devices include SmartPilot for YpsoMate and the YpsoDose large-volume patch injector.

Pharma customers are seeking established platform-based pen and autoinjector platforms that are sustainable and manufactured at multiple sites around the world as therapies become available globally. "Ypsomed is working on processes and new products that will further reduce the device carbon footprint and both improve and increase recyclability," says Mr. Thompson.

The company is focusing on the complete range of platform products and expanding its global manufacturing footprint in Europe, China, and North America. Manufacturing the UnoPen and YpsoMate at multiple sites globally reduces supply chain risks and the ability to manufacture locally is more sustainable. Ypsomed now has more than 70 products on the market and over 130 active customers with many new self-injection device launches planned. ◆

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

KEEPING YOU CONNECTED TO YOUR TARGET AUDIENCE.

For more than 20 years, Drug Development & Delivery has successfully connected technology and service providers with R&D scientists, business development professionals and corporate managers working at pharmaceutical and biotechnology companies.

Marketing your technologies, services and products with Drug Development & Delivery keeps you engaged with your key audience.

Call us today or visit us at drug-dev.com and let us show you how.

- Print & Digital Editions
- Website Marketing
- Email Campaigns
- Videos
- Exclusive Whitepaper & Webinar Marketing
- Online Company Profile
- eBooks
- eNewsletters

John Kiesewetter: 541-338-0022
jkiesewetter@drug-dev.com

Amy Nicklaus: 862-274-5872
anicklaus@drug-dev.com

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

drug-dev.com

Drug Development
EXECUTIVE

Howard Berman, PhD
Founder & CEO
Coya Therapeutics

COYA THERAPEUTICS

Unlocking the Power of Tregs to Combat Inflammation & Fight Neurodegenerative Diseases

Coya Therapeutics, Inc. is a Houston-based clinical-stage biotechnology company developing proprietary treatments focused on the biology and potential therapeutic advantages of regulatory T cells (Tregs) to target systemic inflammation and neuroinflammation. Dysfunctional Tregs underlie numerous conditions, including neurodegenerative, metabolic, and autoimmune diseases. Coya's investigational product candidate pipeline leverages multiple therapeutic modalities aimed at restoring the anti-inflammatory and immunomodulatory functions of Tregs.

Drug Development & Delivery recently had a discussion with Dr. Howard Berman, Founder and CEO of Coya Therapeutics, focusing on how the company is leveraging Tregs, its investigational products and the conditions targeted, Coya's significant partnership with Dr. Reddy's Laboratories, and his goals throughout the next 5 years.

Q: How did you launch Coya? Can you elaborate on your background and how you started the company?

A: I earned a PhD in Neuropharmacology and have spent my career in the pharmaceutical industry. I previously worked at Novartis, Abbvie, and Eli Lilly, where I developed and harnessed skillsets in the areas of drug development and commercialization, learning all of the ropes that now serve me well at Coya. While I was at AbbVie, where I worked prior to launching Coya, my father – a brilliant triple

board-certified physician – started experiencing cognitive loss. Unfortunately, the cognitive loss slowly started to increase in intensity and speed. I took him to see Dr. Stanley Appel, a renowned doctor in the area of amyotrophic lateral sclerosis (ALS) and neurological diseases. At that meeting, Dr. Appel let us know there was not a lot we could do for this condition with the current science and approved products, but asked me to meet him so he could show me what he was working on. He presented me unbelievably exciting data that illustrated that enhancing Treg function and numbers in patients could stop or slow progression in ALS patients and opened up opportunities in other neurodegenerative conditions like dementia, which afflicted my father. Dr. Appel asked me if I would be interested in moving the research initiative forward. After a conversation with my wife, I dropped everything I was doing because I knew that this was too exciting to pass up. And that's when I launched Coya and drove it forward. Two years later, we went through an IPO and became public during the same week my father passed away. I know our company has been blessed from day one, and I attribute those blessings to my father, who has given us success and strength.

Q: How is Coya leveraging Tregs in its pipeline to treat neurodegenerative, autoimmune, and metabolic diseases?

A: Based on the work of Dr. Appel and Houston Methodist, we know Tregs are dysfunctional in neurodegenerative conditions. What we've discovered is that dysfunction in Tregs causes inflammation, which plays a critically important role in a patient's decline and the pathophysiology of neurodegenerative diseases. In addition, we are also focusing on other aspects of the immune system that are compromised by neurodegenerative disease, including the innate immune system and its myeloid cells and macrophages. Our core assets are biologics that repair the Treg dysfunction but simultaneously block other pro-inflammatory pathways, ultimately resulting in synergistic approaches that may keep Tregs durably functional, active, and viable. The key discovery we have made is that inflammation is an important and central driver of these diseases and that Treg cell biology is the common denominator. That is why we are excited about this approach with our COYA 302 investigational product.

Q: Your current lead investigational products are COYA 301 and COYA 302. What specific diseases are they targeting and how far along is Coya to bringing the therapeutics to market?

A: COYA 302 is a combination biologic and our lead asset. We believe combinations are the future of treatment approaches in neurodegenerative diseases, and we're building a pipeline and an asset around COYA 302.

COYA 302 is the combination of our proprietary low-dose interleukin-2 (COYA 301, or LD IL-2) and the immunomodulatory drug CTLA4-Ig, and we believe this combination has the potential to provide a sustained and durable effect the first series of neurodegenerative disorders we are focused on through a targeting of multiple pathways. Our research and clinical efforts have led us to believe that combination biologics using our LD IL-2 as a backbone modality could be the best way to treat neurodegenerative conditions that are inherently driven by a complexity of pathways. We believe COYA 302 represents the most clinically advanced of what we hope will be a family of combination therapies that all feature our LD IL-2.

Moreover, given its growing list of indications, we can now refer to COYA 302 as a "Pipeline in a Product." We are developing COYA 302 for a number of indications. We've previously announced our objective of developing it in ALS. Why ALS? This is a disease driven by a complex set of mechanisms, including dysfunctional Treg biology. COYA 302's combination approach is important to mitigate the underlying biology complexity and is an approach that has been lacking with other investigational agents. In March 2024, we shared new data that highlights the strong predictive value of levels of an oxidative stress biomarker (4-HNE) with the rate of disease progression and survival in 50 ALS patients from a longitudinal patient registry cohort. In a proof-of-concept study in patients with ALS, the combination of LD IL-2 and CTLA4-Ig appeared to lower 4-HNE and other proinflammatory biomarker levels and stop progression at 24 weeks, a key benchmark time point in ALS trials. We believe this is highly promising data.

Also, given our research and clinical findings in a proof-of-concept trial that showed LD IL-2 alone was able to improve cognitive function in Alzheimer's disease (AD) patients after four months of treatment, we recently expanded our pipeline with COYA 302 into Parkinson's disease (PD), Frontotemporal disease (FTD), and AD. While this monotherapy data is clearly encouraging, we believe that treating PD, FTD, and AD patients with our combination therapy of COYA 302, may offer an even

better approach in these patient populations, given what we believe are similar underlying multiple, complex pathways. In the fall of 2023, we completed enrollment of a Phase 2 investigator-initiated trial evaluating LD IL-2 in AD. The results from that trial, expected during the summer of 2024, are expected to serve as the basis for the design of a future trial with COYA 302 in AD patients. Additionally, we anticipate filing an IND in the second half of 2024 to evaluate COYA 302 in patients with FTD and initiating that trial shortly thereafter. Topline data from this Phase 2 trial in FTD is expected in 2025.

Thus, one can see why we now refer to COYA 302 as a "Pipeline in a Product." ALS is our lead indication, but many other larger neurodegenerative patient populations also stand to benefit given the common disease pathways involved.

Q: What makes your pipeline different from other biotech companies looking to combat these diseases?

A: Many biotechs are focused on one neurodegenerative disease, one target, one mechanism, one drug. We believe that is not the correct paradigm nor correct way to target these diseases, as they are complex diseases and not driven by one pathway.

We are moving into the regime of combination approaches and combination biologics, just like the general biotech market has done in cancer, HIV, and viral disease treatment. These combination approaches have transformed the way these diseases are currently treated and have pushed life expectancy out for many years. It's not different in neurodegenerative conditions, in our opinion. Moreover, other companies that are now correctly targeting inflammation as a key pathway driver in neurodegenerative disease are focused on targeting one pathway, which is probably not going to be sufficient, again in our opinion. We are targeting the top of the pyramid of the adaptive immune system, the Tregs, as well as targeting the innate immune system, which is another critically important component of the immune system. By addressing both of these pathways simultaneously, there is the potential to have a disease-modifying treatment that can stop the disease from progressing, whether that be in ALS, PD, FTD, or AD.

Q: What is the significance of Coya's partnership with Dr. Reddy's Laboratories for COYA 302?

A: First, this partnership further validates our approach, the science, the IP, and the commercial opportunity we see with our potential combination therapy platform. Dr. Reddy's Laboratories (DRL) is an independent multi-billion dollar company that did its own deep due diligence and believes in our approach, which is validating.

Second, the partnership is great for ALS patients who are waiting for a more effective treatment for this devastating neurodegenerative disease. Coya and DRL are working seamlessly with our respective strengths to advance COYA 302 as efficiently as possible in ALS.

Third, the partnership strengthens COYA's balance sheet in the short-term and potentially in the mid-term and long-term through this non-dilutive deal worth a potential $700M+. Importantly, DRL received licensing rights only in the ALS indication in the US, Canada, the EU, and the UK, meaning Coya retains the rights to the ALS indication in some key territories (like Japan), as well as all other indications. This provides us with the optionality to execute additional non-dilutive agreements for COYA 302 that can further strengthen the balance sheet.

We executed this deal in a tough biotech environment in 2023, and – when combined with all the clinical and regulatory milestones we achieved in 2023 – demonstrates that we are a company that can execute with an eye on creating value for patients and our shareholders alike.

We are now nearly six months into our partnership with DRL, and we are proud to have the company by our side in our joint effort to bring COYA 302 forward for patients suffering from ALS.

Q: Coya recently licensed intellectual property rights from the University of Nebraska Medical Center for the use of next-generation immune modulatory biologics in combination with COYA 301 to enhance and strengthen Tregs in inflammatory disease. How will Coya utilize this license, and what makes it important?

A: We strongly believe COYA 301 will serve as a backbone for future combination approaches. Similar to COYA 302, there are many other mechanisms that have synergistic potential with LD IL-2. Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF) is one of them. The preclinical data generated to date by

the experts at the University of Nebraska is compelling, as Treg function and numbers are significantly enhanced from the combination of LD IL-2 and GM-CSF, which sets up for applications in many neurodegenerative diseases like PD. This partnership also gives us access to one of the leading experts in the field, and we fully plan to leverage that relationship to advance this combination. Through this partnership, we have the opportunity to enhance our pipeline and potentially enter into strategic partnerships with companies currently developing/manufacturing GM-CSF, providing us additional opportunities for business development deals as well.

Q: What developments do you expect for Coya in the coming five years?

A: There is the near-term, mid-term, and long-term, and I consider five years long-term.

Our near-term objective is to file the IND for COYA 302 in ALS and subsequently initiate the Phase 2 clinical trial in 2024.

Over the mid-term, we expect to have the data readout from that Phase 2 ALS trial with COYA 302 toward the end of 2025 and hope to present a case to the FDA that our drug is safe and efficacious in patients suffering from ALS.

In parallel with the Phase 2 ALS trial, we expect to conduct a Phase 2 trial in patients with FTD and share data from that trial in 2025, also. That data will guide our next steps, including the potential initiation of a subsequent registrational study in FTD, assuming the Phase 2 data supports continued development. The FTD indication also brings additional potential partnership opportunities for us.

We also anticipate advancing COYA 302 in PD and AD in parallel with our ALS and FTD development activities. Moreover, we expect to advance the other assets in our pipeline, including our exosome-based programs that may be ideal for multiple partnering opportunities. ◆

DRUG DELIVERY

Viewing Lipid Nanoparticle Delivery Technology Through the Lens of a CRDMO

By: Lu Tian, PhD

LNP MARKET DYNAMICS

Lipid nanoparticle formulations have undergone remarkable progression in recent few years. To give you just one data point, according to our own internal market analysis, there are now approximately 150 active pipelines that incorporate LNP delivery technologies. What distinguishes this trend is not only its sheer number of pipelines, but also its rapid technological advancement.

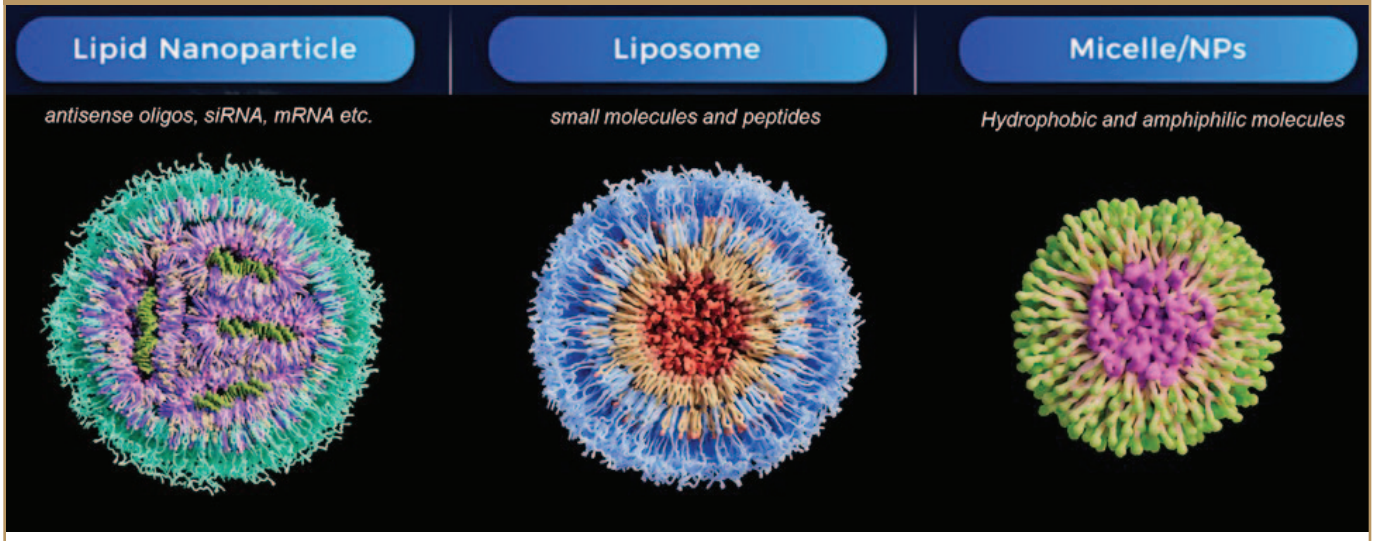
It is also undeniable that the success of mRNA-LNP vaccines against the COVID-19 pandemic stands as a testament to the robustness of this delivery technology. Looking closer, a significant proportion of these pipelines — roughly three-quarters — are RNA-based therapeutics, specifically, LNP delivery supplementing to antisense oligonucleotide, siRNA, and mRNA modalities. Notably, LNP-based COVID-19 vaccines are only the tip of the iceberg of the "LNP club."

So, if we look at advanced pipelines – defined as those that have progressed into late-stage clinical trials – we see targets for a diverse range of indications, such as cancer, endocrine disorders, and even viral infections. And, when we speak with innovators first-hand, we see real confidence in incorporating this delivery system within their newest drug designs. This confidence is anchored by the reliability of LNP formulation in terms of its developability with about 50% of LNP-formulated drugs advancing into the clinical trials.

OVERVIEW OF LNPS

LNPs share a similar concept to liposomes, as demonstrated in Figure 1, in that they involve the encapsulation of an active pharmaceutical ingredients (APIs) within lipid particles that circulate in the bloodstream, ensuring sustained release of the API. What is surprising perhaps is that the current market activity has taken so long to come to fruition. For example, although the inception of PEGylated liposome-based therapeutics dates back to 1995, with the commercialization of Doxil®, the approval of LNP-based therapeutics was delayed by over two decades, marking its breakthrough with Onpattro®'s approval by the FDA in

FIGURE 1



Difference Between LNP, Liposome & Micelle

2018.[1,2]

What has certainly facilitated the recent emergence of LNP as a go-to delivery technology is the evolution of oligonucleotide-based therapeutics. Oligonucleotides used to encounter significant limitations due to their brief circulation time, which arose from serum degradation and limited cellular penetration capability. In this context, LNPs emerged as a robust formulation solution to this problem due to its ability to encapsulate and protect fragile cargoes, safeguarding their transport to target cells and enabling effective release after endocytosis.

Looking closer at their makeup, the fundamental components of LNP vehicles encompass functional lipids and stabilizing lipids.[3] Functional lipids are cationic lipids or ionizable lipids. They play critical functions in cell penetration and release.[4] Cationic lipids in early designs are permanently charged, and although able to effectively bind to the cell membrane and the oligonucleotide API, their cytotoxicity limits their application in LNP design. In contrast, new ionizable lipids exhibit pH sensitivity and maintain a neutral charge in serum. They then become protonated in endosomes, thereby promoting effective endosomal escape of the encapsulated cargo.

The other essential component of LNP vehicles is PEGylated lipids, characterized by their extended PEG polymer heads. These PEG lipids prevent aggregation of LNPs, which enhances their stability and prolongs circulation time within the bloodstream. The incorporation of PEGylated lipids in LNP self-assembly also increases encapsulation efficiency during manufacturing. However, the presence of PEG lipids can present some drawbacks, notably their bulkiness diminishes the affinity of LNPs to ApoE for cellular uptake. A further potential issue is that for patients with established immunity against PEG, the efficacy of drugs with LNP formulation may further decrease. This an ongoing dichotomy that developers face and underscores the intricate balance required when incorporating PEG lipids into LNP formulations.

In addition to the functional lipid and stabilizing PEG lipids, LNP design also incorporates structural lipids, such as cholesterol or phospholipids, and these critical components nowadays have long advanced from natural lipids. Consequently, in the process of new formulation development, fine-tuning of the lipid component selection is necessary. To accommodate the need for precise LNP formulation design, a large library, as demonstrated in Figure 2, with large selection of head groups, linkers, hydrophobic tails, and PEG polymers is a prerequisite for effective LNP development.

COMMON MANUFACTURING APPROACHES

When we turn to look at synthesis, the mainstream manufacturing approaches for LNPs all share the same concepts of mixing, followed by purification and filtration. These methods originate from a simple and quick lab-scale preparation known as ethanol injection, which involves the rapid mixing of a lipid-containing organic phase with an API-containing aqueous solution. However, it initially faced challenges in achieving optimal encapsulation efficiency while ensuring consistent particle size.

The answer was found after extensive research, which showed the crucial role fluidic dynamics and local ethanol concentration play in determining encapsulation efficiency during LNP manufacturing. For example, factors like flow speed, temperature, fluidic mechanics, and ethanol removal rate intricately influence the assembly process. Based on these findings, the modern landscape of LNP manufacturing engineering has diverged into two primary categories: T-mixers and microfluidic mixers.

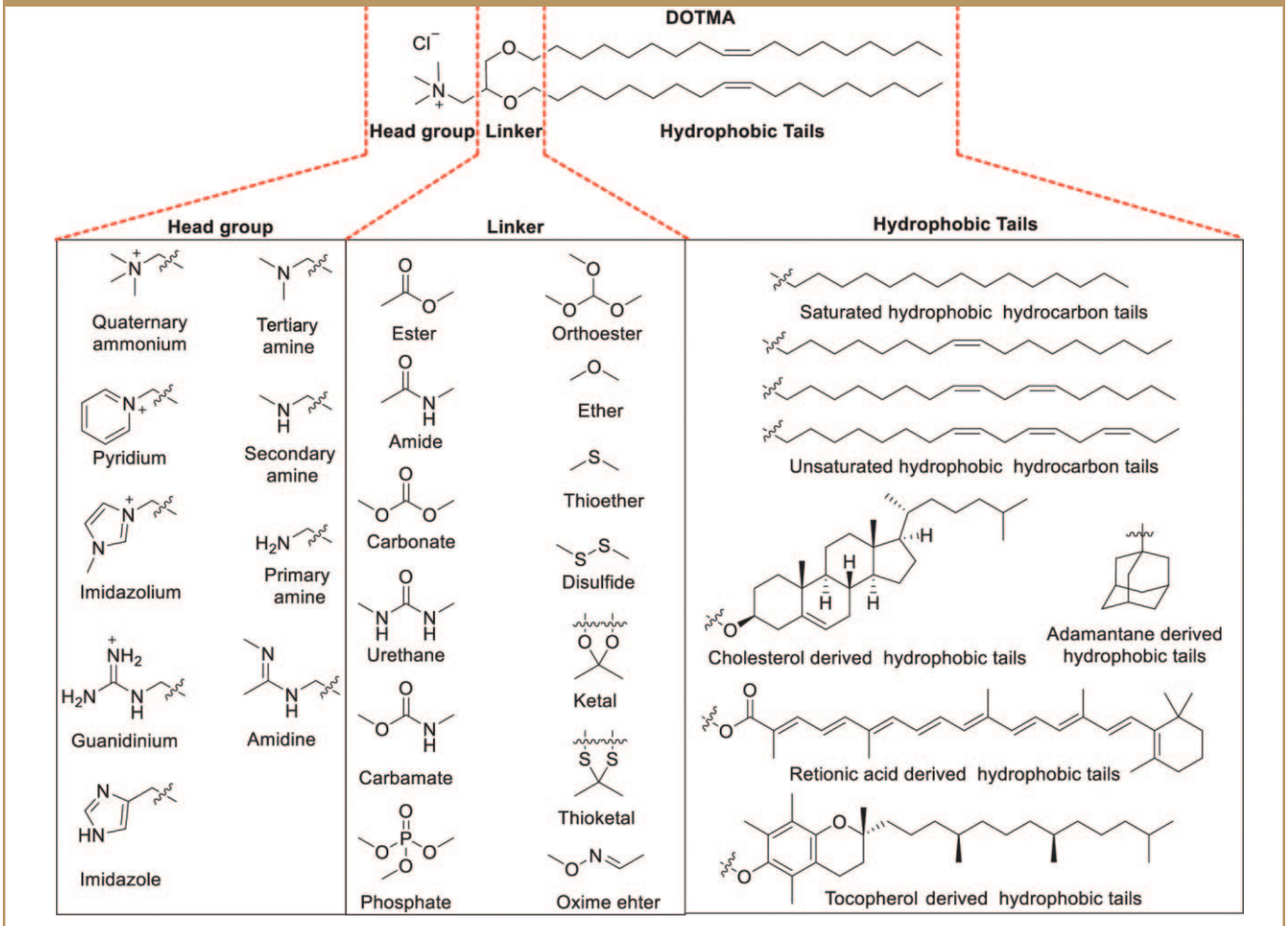
T-mixers are large-scale mixing equipment featuring rapid flow speeds to achieve desirable particle sizes. This approach has remarkable advantages of simplicity, efficiency, scalability, and consistent quality. Notably, the T-mixers have been implemented in the manufacturing of prominent LNP-based drugs such as the mRNA vaccines.

In contrast, microfluidic mixers operate at the microscopic level, meticulously managing fluid dynamics to ensure precise and high-quality mixing. An illustrative example is WuXi STA's multi-channel microfluidic mixer, equipped with multiple inlet valves. These valves supply solutions that are not only limited to conventional ethanol and aqueous solutions, but also other materials such as polymers, salts, and ligands for conjugation. It also offers adjustable parameters similar to flow chemistry reactors, enabling precise manipulation of reactions. Such a system is a powerful tool for advanced LNP formulation at a scalable level.

LNP & CONJUGATES – ADVANCED LNP MANUFACTURING

As previously mentioned, LNPs share physiological similarities to liposomes, with

FIGURE 2



WuXi STA offers customized lipid design, as well as common commercial lipids in stock as catalogs.[5]

a natural affinity to ApoE; and unconjugated LNPs already have specificity for hepatic cells and facilitate efficient internalization. Therefore, for hepatic indications or those that do not require a specific target cell type, this intrinsic property eliminates the need for additional targeting agents in LNP formulations. In addition, studies hint at ApoE's role in brain lipoprotein scavenging. The utilization of this pathway is therefore highly promising for siRNA-LNP therapeutics against brain indications, but no pipeline with this design has yet advanced to NDA submission.

In contrast, for tissues that do not utilize the ApoE metabolism pathway, unconjugated LNP is futile, and in response, the conjugation of ligands, such as antibodies, has emerged as a potent strategy to enhance LNP targeting. By incorporating ligands onto the LNP surface, the ability to recognize and interact with specific target molecules is magnified. This approach introduces three methods: direct assembly, post-modification, and post-insertion.

Direct assembly involves integrating the ligands during the self-assembly mixing process, demanding specialized mixers and amphipathic ligands, often heavily modified. The tremendous size of common ligands severely impairs the efficiency of the self-assembly process. Therefore, small molecule (eg, shorter peptide) ligands are more favorable for this method.

Conversely, post-modification/insertion methods introduce the ligands after LNP vesicle assembly. This process involves the incorporation of the heterobifunctional PEG lipid anchors on the LNP surface during the initial assembly of the LNP. While ligands are clicked on these PEG lipids via azide-mediated ligation, after the assembly. Such design is already being tested on some siRNA-LNP pipelines.[6]

Despite remaining in preclinical phases, LNP-conjugate designs stand as a beacon of hope for future drug delivery strategies. Particularly promising for RNAi-related therapeutics, these innovations hold the potential to expand the indication selection by enhancing the efficacy and precision of LNP-mediated drug delivery.

LNP QUALITY ATTRIBUTES & CMC CONSIDERATIONS

Most LNP formulations are sterile injectables and thus are require to follow ICH Q8 R2 guidelines in the CMC process. However, for LNP formulations, there are still specific quality control considerations for effective development.

The balance of different lipid components significantly impacts the API encapsulation and nanoparticle assembly. And, this factor serves as the indicator of the quality of LNP products. Achieving the optimal ratio of lipid components is essential, not only for encapsulating the API effectively, but also for determining the LNP's overall stability and performance.

Particle size distribution stands as another vital aspect of LNP quality control. The size distribution influences in-vivo release dynamics and ultimately the delivery efficiency. Also, *in-vitro* release testing is one of the key evaluations before preclinical evaluation. From this, developers gain a crucial understanding of the interaction between LNP and its cargo, before proceeding to animal PK studies. This insight provides a crucial opportunity for developers to make the most cost-efficient decisions.

In addition to the lipid component composition and LNP particle analysis, several other attributes should be considered and examined extensively for a successful formulation. Leachable and extractable studies are especially important for LNPs because of their pH sensitivity. The fill-to-delivered volume ratio reflects the osmolality and ultimately the delivery efficiency. Additionally, attributes such as sterility and endotoxin levels simply reflect the quality of the manufacturing process – therefore, good CMC practices with comprehensive analytical capabilities are fundamental for a successful LNP formulation.

THE IMPORTANCE OF INTEGRATED CAPABILITIES FOR LNP DEVELOPMENT

The complexity of LNP formulations demands diverse and integrated capabilities for development – incorporating lipids, oligonucleotides, small molecules, and sometimes antibodies or ligand, and thus it requires a cohesive approach. Additionally, a comprehensive analytical platform with specialized testing for LNPs is also a must for development and further regulatory applications. So, with this as the technology's background, it is perhaps unsurprising that seeking partnership is the de facto approach for a majority of developers in LNP-based therapeutics.

Ideally, an established LNP platform by a CRDMO should cover the entire journey of the therapeutic's development, including lipids/oligonucleotide research, LNP development, API and drug product manufacturing, and proper analytical work. This synergy ensures the seamless amalgamation of components, forming the bedrock of a successful formulation. With LNP development projects, each decision has consequences and shapes the trajectory of the final product. So developers more than perhaps in many other areas have to rely upon their partners to bring in the needed development expertise. Without prior experience, development will not be able to progress at the required rate and likelihood of achieving optimal results is reduced.

In fact, what sets successful CRDMOs apart is not only this experience but also access to cutting-edge manufacturing equipment coupled with specialized analytical supports. With an LNP, your development is only as strong as its weakest link – so it's important that going into a partnership you find a CDMO that will not only offer services but is more of a strategic development enabler. With comprehensive capabilities, expert decision-making, and advanced infrastructure, CRDMOs play an indispensable role in translating LNP innovations into impactful therapeutics, benefitting patients around the world. ◆

REFERENCES

1. "Doxil Prescribing Information." Pfizer, 1974, https://labeling.pfizer.com/showlabeling.aspx?id=530#:~:text=DOSAGE%20AND%20ADMINISTRATION,symptoms%20of%20cardiomyopathy%20(2.2). Accessed 5 October 2023.
2. "Onpattro Prescribing Information." Alnylam Pharmaceuticals, 2018, https://www.alnylam.com/sites/default/files/pdfs/ONPATTRO-Prescribing-Information.pdf. Accessed 31 October 2023.
3. Albertsen Hald C, Kulkarni JA, Witzigmann D, Lind M, Petersson K, Simonsen JB. "The role of lipid components in lipid nanoparticles for vaccines and gene therapy." Adv Drug Deliv Rev 188 (2022): 114416. https://doi.org/10.1016/j.addr.2022.114416
4. Sun D, Lu ZR. "Structure and Function of Cationic and Ionizable Lipids for Nucleic Acid Delivery." Pharm Res 40.1 (2023): 27-46. https://doi.org/10.1007/s11095-022-03460-2
5. Zhang Yuebao, Sun Changzhen, Wang Chang, Jankovic Katarina E, Dong Yizhou. "Lipids and Lipid Derivatives for RNA Delivery." Chemical Reviews 121.20 (2021): 12181-12277. https://doi.org/10.1021/acs.chemrev.1c00244
6. Swart LE, Koekman CA, Seinen CW, Issa H, Rasouli M, Schiffelers RM, Heidenreich O. "A robust post-insertion method for the preparation of targeted siRNA LNPs." International Journal of Pharmaceutics 620 (2022): 121741. https://doi.org/10.1016/j.ijpharm.2022.121741

BIOGRAPHY

Dr. Lu Tian is Senior Director, LNP platform lead & CMC Project Management at WuXi STA. He earned his PhD in Chemistry from Rutgers University. He has extensive experience in novel drug development having spent over 4-years at STA and the preceding decade in roles at InnovForm Therapeutics, Merck, and Abbott Laboratories. At STA he leads a dedicated team on the development and implementation of WuX's market leading suite of LNP technologies.

Respiratory Drug Delivery Conferences

Delivering Pulmonary and Nasal Insights and Excellence for 35 Years

RDD®

Conferences attract 500 academic, commercial, and government delegates from more than 25 countries

25+ Expert Speakers
75+ Posters
60+ Exhibitors
12 Workshops

Over 2,800 peer-reviewed, inhalation-focused, searchable papers provide lasting visibility and impact

Data from RDD 2022

Key opinion leaders present scientific, engineering, clinical, regulatory and commercial insights of immediate and lasting value in business-friendly venues offering exceptional networking.

Participate in the premier international conference series with a reputation for facilitating connections and delivering know-how in drug delivery to the lungs and nose.

Novel Targets & Treatments | Formulation & Device Innovation
Manufacturing & Industrialization | Navigating Nasal | Regulatory Science
Advanced Data Analytics | Connectivity | Sustainability

ATTEND | **PRESENT** | **EXHIBIT** | **SPONSOR**

Deadlines and details: rddonline.com | Questions: info@rddonline.com

SILICON-STABILIZED HYBRID LNPS

Next-Generation Delivery of RNA Therapeutics

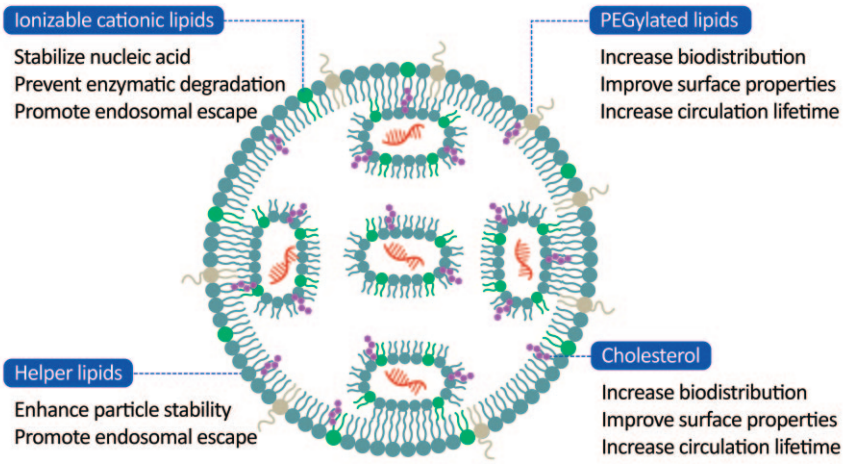
By: Suzanne Saffie-Siebert, PhD, Michael Welsh, PhD, Nissim Torabi-Pour, PhD, and Flavia M. Sutera, PhD

INTRODUCTION

In recent years, lipid nanoparticles (LNPs) have revolutionized the field of nucleic acid therapeutics by overcoming significant challenges in the cellular delivery of DNA and RNA. They particularly rose to prominence as the mRNA delivery technology in the Moderna and Pfizer/BioNTech COVID-19 vaccines, but they are also being applied in over 200 ongoing clinical trials of other RNA-based drugs.[1-4]

Despite these impressive successes, current LNP formulations face some recognized limitations that are critical to overcome if we are to see improved clinical translation of RNA-based therapeutics.[5] These can be briefly summarized as stability, safety, targeting, and transfection efficiency. The following sections will consider these current shortcomings, as well as some accompanying manufacturing challenges, and will show how they can be addressed by SiSaf's silicon-stabilized hybrid LNPs (sshLNPs), marketed under the trade name of Bio-Courier®.

FIGURE 1



Schematic representation of lipid nanoparticles for nucleic acid delivery, highlighting the role of each of the four major components.

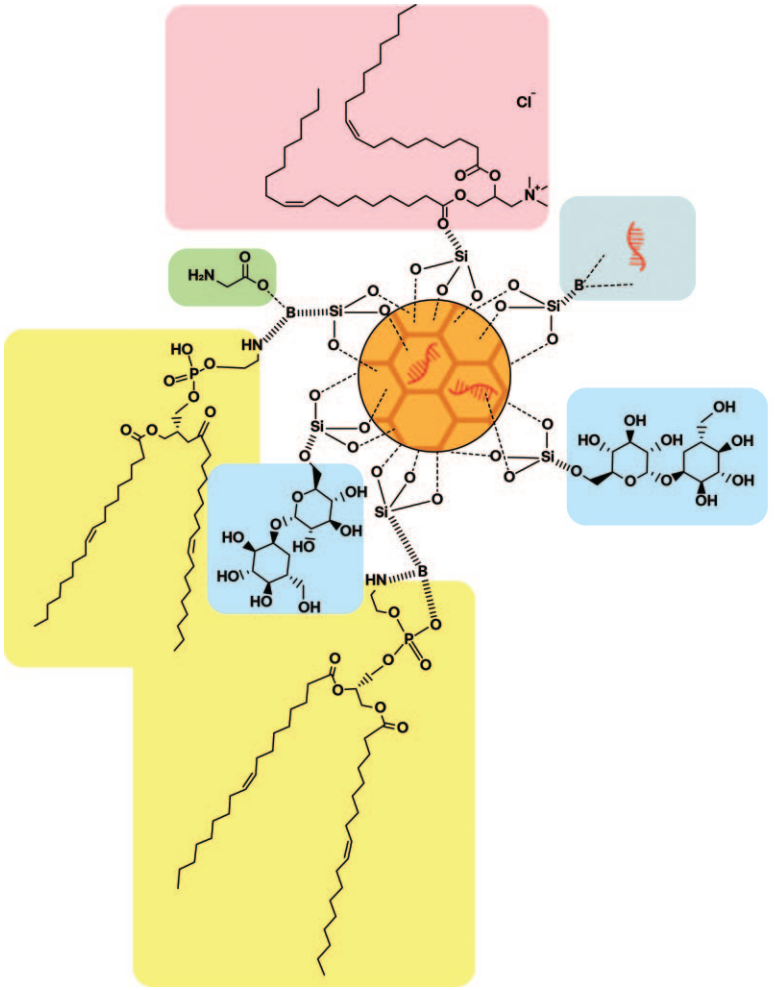
LNPS & SSHLNPS

In general, the LNPs used to deliver nucleic acid therapeutics consist of four key components: ionizable or cationic lipids, helper lipids, PEGylated lipids, and cholesterol (or a related compound). A general schematic illustrating the role of each of these components is shown in Figure 1. Importantly, the exact nature of the constituents used in a given LNP formulation will define its physical, chemical, pharmacokinetic, and pharmacodynamic properties.

In recent years, intensive research has enabled fine-tuning of these characteristics for various therapeutic contexts, but to date, only a small subset of reported components has been licensed for use in drug delivery formulations.[6] Considerable optimization work may also be necessary, as illustrated by the case of patisiran (the first FDA-approved siRNA therapy delivered using LNPs), in which over 300 ionizable lipids were screened in developing the final formulation.[7]

Bio-Courier sshLNPs combine organic lipids with inorganic hydrolyzable silicon (Figure 2). The silicon matrix stabilizes both the lipid components and the RNA payload, reducing or completely removing the need for ionizable or cationic

FIGURE 2



Schematic representation of silicon-stabilized lipid nanoparticles ("Bio-Courier") for nucleic acid delivery.

lipids, PEGylated lipids, or cholesterol.[8-11] As we will show, this addresses some of the safety concerns associated with current LNP formulations and can also improve targeting and transfection.

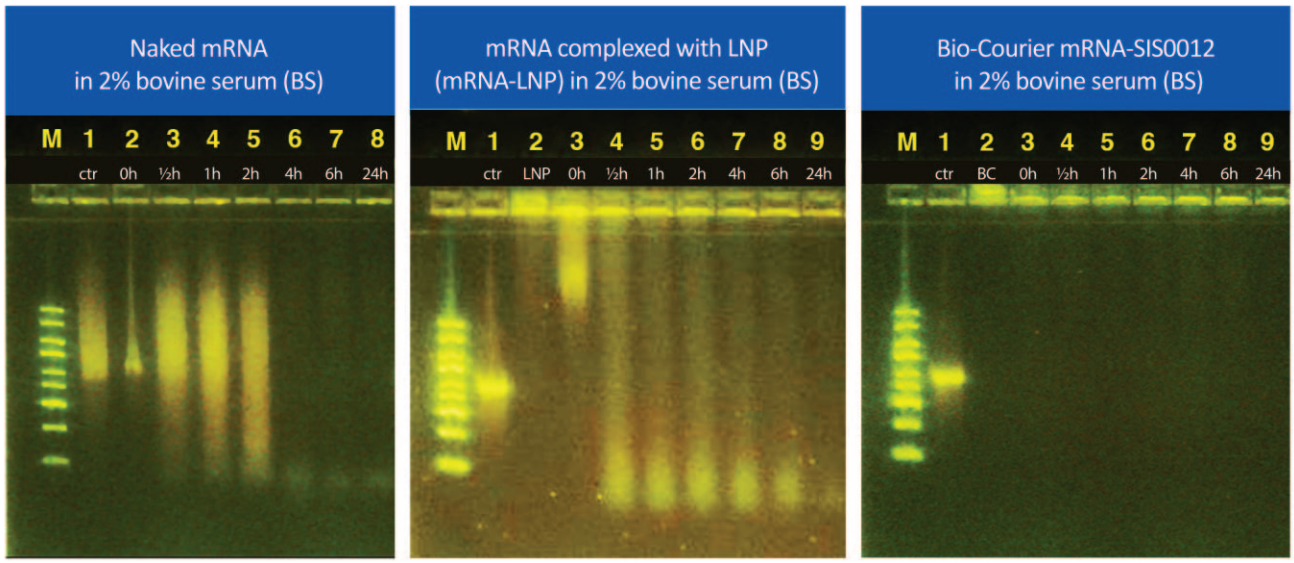
KEY CHALLENGE #1: STABILITY

The stability of LNPs inevitably impacts the efficacy and safety of the administered therapy. It depends on both the overall structural integrity of the particles and the chemical stability of the individual constituents, either in storage or upon exposure to biological fluids. The large-scale international rollout of COVID-19 mRNA vaccines highlighted some obvious shortcomings of existing technologies for clinical application of LNPs, especially in the requirement for storage at ultralow temperature and the limited shelf life.[12,13]

Typically, LNPs and liposomes incorporate lipid and phospholipid components that contain ester linkages. These are prone to chemical hydrolysis (particularly under acidic or basic conditions), meaning ester hydrolysis can be a limiting factor for stability and shelf-life of lipid-lipid systems stored in aqueous solution.[14] Ester linkages are also prone to enzymatic degradation in vivo by esterases, as shown in a recent pharmacokinetic study by Moderna that investigated the metabolic fate of "Lipid 5", a commonly used ionizable lipid component in LNPs for preclinical studies.[15] In contrast, Bio-Courier technology is able to decrease chemical hydrolysis of ester linkages in lipid constituents via silicon-lipid binding (Figure 2).

Relatedly, a notable study by Packer et al identified inactivating lipid-RNA adducts in COVID 19 mRNA vaccines, formed via oxidation of the ionizable lipid component followed by reaction with the RNA.[16] The proposed mechanism could apply to all LNPs containing ionizable lipids, and as a result, testing for these impurities is expected to be incorporated into future QC protocols.[17] Other investigators have observed significantly lower protein expression after exposure of mRNA-loaded LNPs to fluorescent lighting, suggesting photochemical degradation of the encapsulated

FIGURE 3



Enhanced protection of encapsulated mRNA for Bio-Courier sshLNPs (right) vs. LNPs (center), compared with naked mRNA (left). Samples were incubated at 37°C as indicated. "M" = marker lane; "ctr" = control; "BC" = Bio-Courier.

RNA under conditions that may be relevant to clinical practice. These findings, together with other unanswered questions regarding the current formulations, have naturally accelerated the search for improved technologies. In an important recent example, Meulewaeter et al described the development of a novel lyophilized LNP formulation that maintained in vivo mRNA transfection efficiency after 12 weeks at room temperature.[17-20]

Superior physical stability is a core feature of Bio-Courier sshLNPs. Unlike LNPs formulated without silicon, they maintain their original polydispersity index (PDI) after multiple cycles of high shear force extrusion that induce repeated mechanical stress. In addition, sshLNPs sshLNPs preserve their original zeta potential for at least 6 months at room temperature (indicating surface structural stability), whereas a significant decrease was seen for standard LNPs after only four weeks under the same conditions. There is also evidence for improved RNA protection with sshLNPs. In one such test, a representative Bio-Courier formulation was able to fully protect mRNA against degradation in bovine serum for at least 24 h at 37°C (Figure 3).

KEY CHALLENGE #2: SAFETY & ADVERSE REACTIONS

It is vital to ensure the encapsulated RNA does not leak from LNPs into the systemic circulation. This would cause unwanted inflammatory and immune responses due to "naked" RNA exposure, emphasizing the importance of physical LNP stability.[21] While such leakage is largely avoided with current formulations, the use of PEGylated lipids represents a long-standing safety concern, despite the fact they are universally incorporated into the existing approved LNPs for RNA delivery.

Originally, PEGylated lipids were introduced as a "stealth sheath" to shield the particles from protein binding and prevent aggregation, thereby reducing clearance and extending plasma half-life.[4,21] It is now also recognized they make a key contribution to LNP stability; but on the other hand, PEGylation reduces the cellular uptake and transfection efficiency of RNA-loaded LNPs.[22,23] The current solution to balance these conflicting properties is to use "sheddable" PEG lipids, with variation of the carbon chain length of the lipid portion such that the PEGylated component gradually dissociates from the LNP at an optimal rate, representing the best trade-off between particle stability and clearance.[21,24]

Even with a carefully controlled serum half-life, PEGylated lipids can still induce anti-PEG antibodies and provoke an immune response.[25] Moreover, antibody binding to PEGylated LNPs can prematurely release part of the mRNA payload, potentially exacerbating clinical hypersensitivity reactions that can range from mild to severe, or even be life-threatening.[26-29] For situations requiring repeat administration, anti-PEG antibodies may lead to more rapid clearance of the drug product and significantly reduce its efficacy.[30] And although it is rarely addressed in the context of LNPs, PEG polymers are notoriously

prone to oxidation, for example, through the action of serum alcohol dehydrogenase.[31,32]

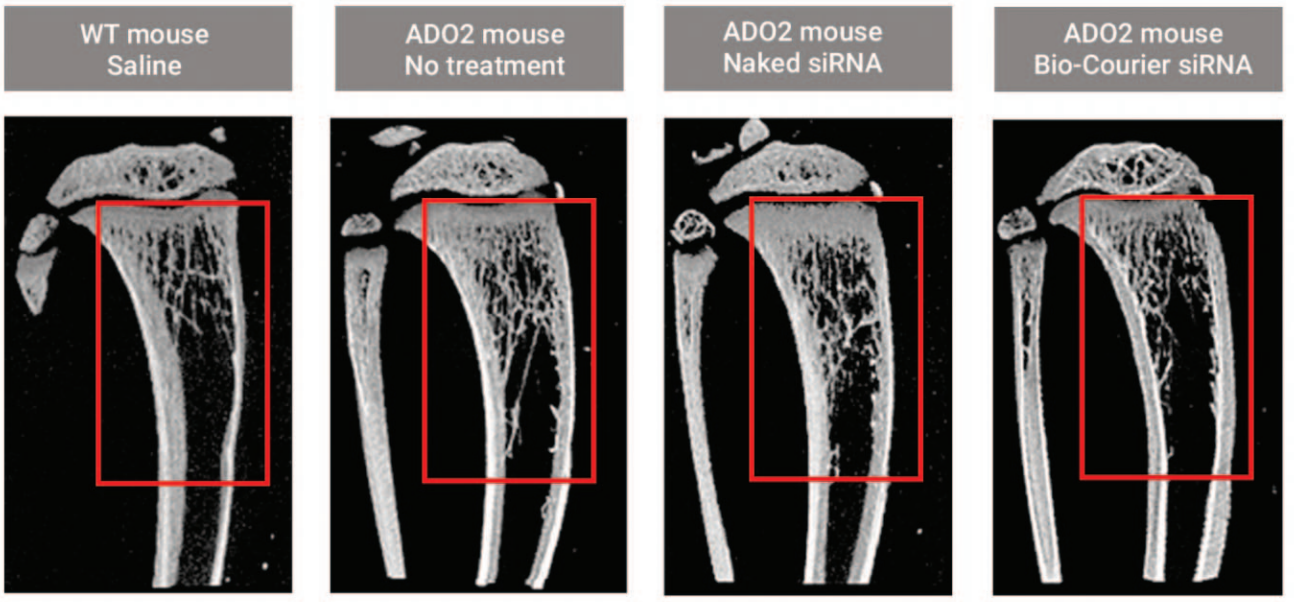
Unsurprisingly, the aforementioned shortcomings have stimulated an active search for PEG alternatives. In a notable recent study by BioNTech, polysarcosinylated LNPs exhibited lower inflammatory and immune responses than their PEGylated equivalents when used for mRNA delivery.[33] Another interesting strategy is polysialylation, which has already been applied in clinical trials of polysialylated therapeutic proteins without evidence of immunogenicity, and did not induce antibodies when used as an alternative to PEGy-lation for liposomes.[34,35]

It is also important to consider the ionizable lipid component. Early LNP formulations used permanently charged cationic lipids to achieve nucleic acid delivery, but although they resulted in efficient transfection, their significant cytotoxicity and immunogenicity soon became clear, and proinflammatory effects were often observed.[5,36,37] These findings inspired development of more biocompatible ionizable lipids that are neutral at normal physiological pH but become positively charged under the more acidic conditions in late endosomes, thereby promoting escape and cytoplasmic delivery of the RNA payload.[38]

Because they represent a key milestone for clinical success of LNP-mediated RNA delivery, ionizable lipids have remained a major research focus in the field and are now known to also influence cellular uptake.[39,40] Nevertheless, some safety concerns remain, as illustrated by the Packer et al. study mentioned earlier, which identified inactivating lipid–RNA adducts in COVID-19 mRNA vaccines (linked to oxidation of the ionizable lipid component).[16,41] Another group found highly proinflammatory effects of LNPs used in preclinical COVID-19 vaccine studies, which were specifically attributable to the ionizable lipid component (likely referring to the ALC-0315 lipid used in the final Pfizer/BioNTech product 6). In addition, ionizable lipids appear to modulate immune responses to LNPs in ways that are not yet well understood.[37,38,42] The ability of LNPs to act as both delivery vehicles and adjuvants offers important opportunities, but it will be important to find an optimal balance between the positive adjuvant and negative proinflammatory properties as the field of mRNA vaccines moves forward.

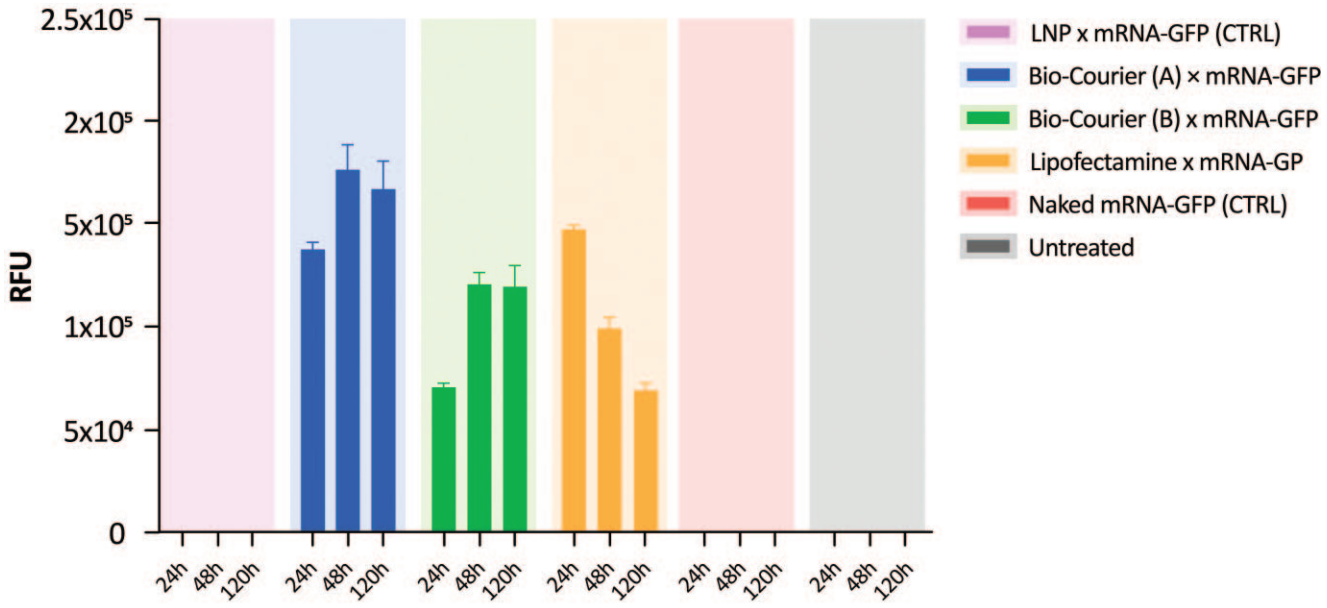
At SiSaf, we created our organic-inorganic hybrid sshLNPs as a well-balanced delivery system to help address this need. Due to their silicon-stabilized design, they are less reliant on PEGylated lipids than conventional LNPs, to the extent that some formulations are entirely free of PEGylation. As well as circumventing the potential aforementioned adverse effects, this makes sshLNPs more compatible with lyophilization and avoids the requirement for cold supply chain distribution. Moreover, compared with existing delivery vehicles that contain cationic lipids (such as liposomes), the silicon stabilization of Bio-Courier may enhance transfection efficiency through alternative surface charge

FIGURE 4



ADO2 mice treated with SiS-012 sshLNPs loaded with 4 mg/kg of Clcn7G213R-siRNA showed a rescue of the bone phenotype.

FIGURE 5



Human primary cells were transfected with two different Bio-Courier formulations delivering GFP-encoding mRNA. Transfection was compared with a LNP formulation and with a commercial transfection reagent, Lipofectamine. Readings were performed at 24 h, 48 h, and 120 h. Error bars represent the standard deviations calculated from three independent biological replicates. The LNP formulation and the naked mRNA–GFP achieved no transfection, while the two Bio-Courier formulations achieved comparable or better transfection than Lipofectamine.

functionalization (by using doped silicon), thus reducing the cationic lipid requirements. Finally, the hydrolyzable silicon component of sshLNPs is designed to degrade in vivo to 100% biocompatible orthosilicic acid, which is readily excreted in the urine and has no known safety concerns.[43,44]

KEY CHALLENGE #3: TISSUE-SPECIFIC TARGETING

It is well established that LNPs have a strong tendency to accumulate in the liver due to interaction with apolipoprotein E and consequent uptake by hepatocytes, mediated primarily via the low-density lipoprotein receptor (LDLR).[45,46] Importantly, overcoming this limitation was recently identified as a critical factor for future growth of LNP-enabled nucleic acid therapeutics.[47] While current formulations do allow for LNPs to be directed to spleen or lung in addition to the liver, tissue- or organ-specific targeting beyond this remains a considerable challenge and generally requires optimization on a case-by-case basis.[48]

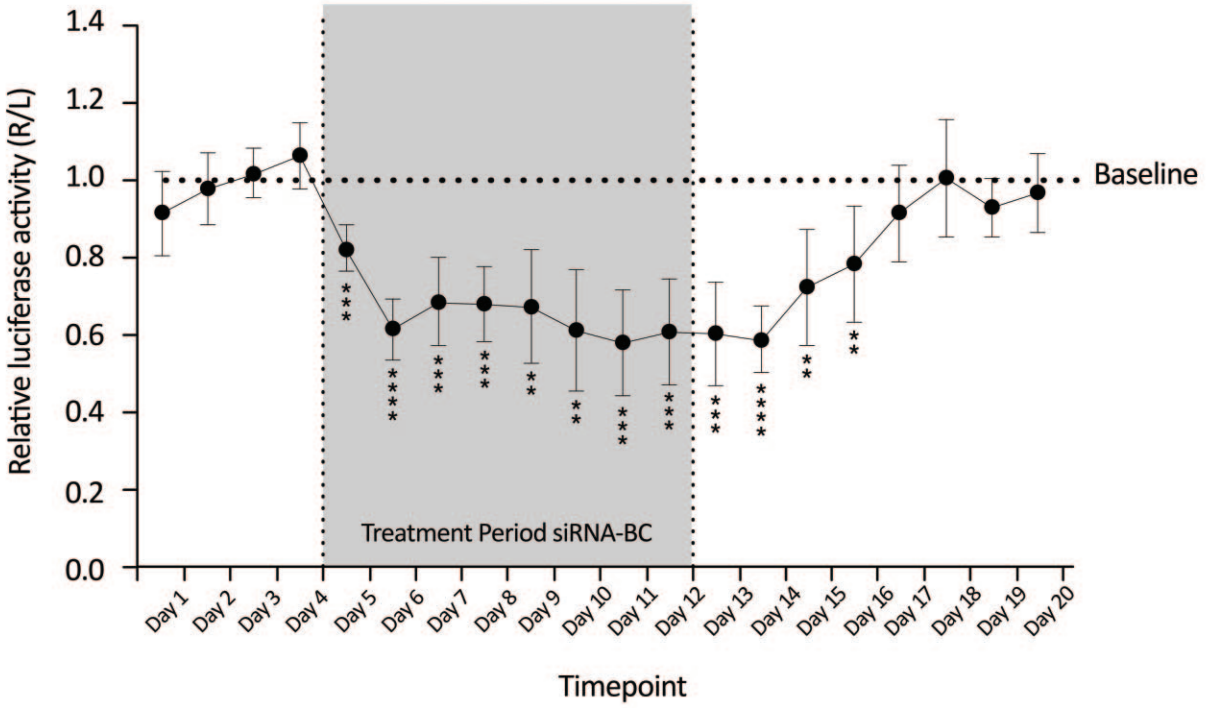
One reason for this complexity is the formation of a biomolecular corona around LNPs after administration, through binding of endogenous proteins and lipids to the particles on entering the circulation. This can significantly impact the pharmacokinetics, tissue distribution, and targeting characteristics of the formulation in ways that are difficult to predict. For example, Huayamares et al. screened nearly 100 distinct LNPs to achieve targeted mRNA delivery to tumors without significant liver accumulation.[49,50]

Bio-Courier formulations can readily be customized, for example, through adjusting the freely modifiable PEGylated lipid content (which can be zero). In principle, this means that more effective tissue targeting may be possible than for standard LNPs, and we have already obtained some evidence for this. In a mouse model of autosomal dominant osteopetrosis type 2 (ADO2), which is caused by heterozygous loss-of-function mutations in the CLCN7 gene, Bio-Courier sshLNPs were able to successfully deliver siRNA to femur, to silence the mutant allele and fully restore normal bone density (Figure 4).[51]

KEY CHALLENGE #4: TRANSFECTION EFFICIENCY

Robust transfection of target tissues requires both cellular uptake and endosomal escape of the nucleic acid payload, and the low efficiency of the latter remains a major bottleneck for LNP-mediated delivery of therapeutic RNA.[40,49] In this regard, ionizable lipids have received the most attention due to their previously explained central role, but recent work has also established the cholesterol compo-

FIGURE 6



Mice expressing cornea-specific firefly luciferase under control of the Krt12 promoter were treated topically once a day with Bio-Courier (BC) sshLNPs containing luciferase siRNA (right eye; R) or control siRNA (left eye; L). No histological abnormalities were seen after multiple treatments.

nent as a major factor. By developing a reporter system to visualize endosomal escape, Herrera et al demonstrated that C24 substituted sterols — particularly β-sitosterol — were much more effective at inducing cytoplasmic delivery of mRNA than unmodified cholesterol.[40] Other notable work has established the particle size of LNPs as a major determinant of transfection efficiency, highlighting the importance of robust structural integrity for LNPs intended for clinical use.[52] These findings are also reflected in the FDA's critical quality attributes (CQAs) for liposome drug products, which include particle size and size distribution.[53]

On a different note, two recent studies have revealed a seemingly underappreciated role for clearly defined stereochemistry in LNP constituents. More specifically, LNPs formulated with stereochemically pure 20α-hydroxycholesterol were found to deliver mRNA three times as efficiently *in vivo* as those containing mixed isomers, as a result of reduced phagocytic sorting.[54] Similar results have just been reported for a chiral ionizable lipid, strongly suggesting that stereochemical integrity is a critical functional factor for LNPs, in line with what has long been known for small-molecule drugs.[55]

Significantly, the improved physical stability of sshLNPs translates into improved RNA delivery both *in vitro* and *in vivo*. In hard-to-transfect human primary cells, standard LNPs failed to deliver an mRNA encoding GFP, while Bio-Courier was able to match the performance of a widely used commercial transfection reagent (Figure 5).[56] Furthermore, the Bio-Courier formulations led to sustained transfection for at least five days, unlike the commercial reagent.

For *in vivo* delivery, topical ocular administration of an siRNA-loaded Bio-Courier formulation was found to induce robust corneal gene silencing in luciferase reporter mice (Figure 6).[57]

KEY CHALLENGE #5: MANUFACTURING

For LNP-mediated delivery of RNA therapeutics, the major logistical challenge is the inherent chemical instability of the RNA itself.[12] It may be possible to offset this through future advancements, such as further development of the formulation recently described by Meulewaeter et al, but maintaining RNA integrity currently poses a major problem for clinical applications.[20] The issue partly stems from the fact that in existing protocols, the nucleic acid payload must be introduced early in the production process during initial formation

of LNPs, prior to subsequent purification and fill/finish steps.[58,59] In this approach, the LNPs are effectively formed around the nucleic acid cargo because it cannot easily be introduced later. This limitation not only restricts batch sizes in commercial manufacturing due to the chemical lability of RNA, it also affects the quality of the product that ultimately reaches the patient.[60]

For example, the Pfizer BNT162b2 COVID-19 vaccine is estimated to lose around 30% of its initial RNA integrity during the production process, with further deterioration expected during distribution and storage — even with an ultracold supply chain.[61] Therefore, alternative manufacturing technologies are urgently needed if the full potential of RNA therapeutics is to be realized.[62]

SiSaf's sshLNPs offer a significant advantage in this regard because the presence of the silicon component means they remain amenable to nucleic acid encapsulation after initial assembly. In contrast to conventional LNPs, Bio-Courier formulations can be manufactured "empty" and loaded with the desired therapeutic RNA later, at the desired point and time of use. This key difference eliminates the requirement for a cold supply chain since lyophilized or liquid sshLNPs can readily be shipped, reconstituted (if lyophilized), and loaded at ambient temperature. In long-term storage tests, non-lyophilized Bio-Courier sshLNPs maintained their original size and zeta potential for at least 6 months at room temperature and 24 months at 4°C, which was much longer than for conventional LNPs (<12 weeks). Thus, RNA encapsulation and fill/finish operations may be separated from initial manufacture by considerable time and distance, readily permitting on-demand preparation of customized RNA-loaded LNPs on any scale, and at any required dosage for customized patient treatment.

This capability largely eliminates the potential safety and efficacy concerns associated with gradual degradation of RNA during manufacture, distribution, and storage of current formulations. It also opens up previously inaccessible use cases; for example, in personalized medicine (such as cancer mRNA vaccines) or for treatment of geographically constrained diseases.[63] The decoupling of RNA encapsulation and LNP formation can significantly reduce costs and environmental impact (e.g., energy demand), and can expand global accessibility to locations where cold chain logistics are not viable. Thus, sshLNPs come with some significant differentiators from current supply chains that mean they could revolutionize the field of nucleic acid medicines.

SUMMARY & OUTLOOK

The global RNA therapeutics market is projected to grow from around $5 billion in 2021 to $25 billion by 2030, yet this relies substantially on improved formulations to maximize the potential of these drugs. While the longstanding use of LNPs in the clinic has firmly established their safety and applicability as a delivery mechanism of choice for nucleic acid drugs, it has also highlighted some important outstanding challenges, such as stability (including storage stability), safety, the targeting of tissues beyond the liver, and the need for RNA encapsulation during LNP formation.[64] The hybridization of organic lipids with inorganic biodegradable silicon in Bio-Courier formulations offers potential for improved clinical performance, while reducing the rate of adverse reactions and improving patient safety. As sshLNPs do not require RNA to be encapsulated during initial LNP formation, they open up this line of therapeutics globally without compromising on added energy costs for ultracold transport and storage. This enables an easily accessible kit-based approach, allowing growth of the RNA field not only in vaccines but also in personalized medicine. ◆

REFERENCES

1. Wang C, Zhang Y, Dong Y. Lipid nanoparticle–mRNA formulations for therapeutic applications. Acc Chem Res. 2021;54(23):4283–4293. https://doi.org/10.1021/acs.accounts.1c00550.
2. Curreri A, Sankholkar D, Mitragotri S, Zhao Z. RNA therapeutics in the clinic. Bioeng Transl Med. 2023;8(1):e10374. https://doi.org/10.1002/btm2.10374.
3. Hou X, Zaks T, Langer R, Dong Y. Lipid nanoparticles for mRNA delivery. Nat Rev Mater. 2021;6(12):1078–1904. https://doi.org/10.1038/s41578-021-00358-0.
4. Kumar R, Chalarca CFS, Bockman MR, et al. Polymeric delivery of therapeutic nucleic acids. Chem Rev. 2021;121(18):11527–11652. https://doi.org/10.1021/acs.chemrev.0c00997.
5. Moss KH, Popova P, Hadrup SR, Astakhova K, Taskova M. Lipid nanoparticles for delivery of therapeutic RNA oligonucleotides. Mol Pharm. 2019;16(6):2265–2277. https://doi.org/10.1021/acs.molpharmaceut.8b01290.
6. Paunovska K, Loughrey D, Dahlman JE. Drug delivery systems for RNA therapeutics. Nat Rev Genet. 2022;23(5):263–280. https://doi.org/10.1038/s41576-021-00439-4.
7. Kulkarni JA, Witzigmann D, Chen S, Cullis PR, van der Meel R. Lipid nanoparticle technology for clinical translation of siRNA therapeutics. Acc Chem Res. 2019;52(9):2435–2444. https://doi.org/10.1021/acs.accounts.9b00368.
8. Saffie-Siebert RS, Torabi-Pour N, Ahmed N, inventors; SiSaf Limited, assignee. A delivery system comprising silicon-containing material. WIPO Patent Application WO 2020/193995 A1. March 30, 2020.
9. Saffie-Siebert RS, Baran-Rachwalska PM, Sutera FM, Torabi-Pour N, inventors; SiSaf Limited, assignee. A delivery system comprising silicon nanoparticles. WIPO Patent Application WO 2020/193999 A1. March 30, 2020.
10. Saffie-Siebert RS, Ahmed M, Sutera F, inventors; SiSaf Limited, assignee. Compositions comprising doped silicon particles, and related methods. WIPO Patent Application WO 2023/002222 A1. July 22, 2022.
11. Saffie-Siebert RS, Welsh M, Torabi-Pour N, inventors; SiSaf Limited, assignee. Nucleic acid vector compositions. WIPO Patent Application WO 2023/002223 A1. July 22, 2022.
12. Schoenmaker L, Witzigmann D, Kulkarni JA, et al. mRNA–lipid nanoparticle COVID-19 vac-

cines: Structure and stability. Int J Pharm. 2021;601:120586. https://doi.org/10.1016/j.ijpharm.2021.120586.
13. Zhao P, Hou X, Yan J, et al. Long-term storage of lipid-like nanoparticles for mRNA delivery. Bioact Mater. 2020;5(2):358–363. https://doi.org/10.1016/j.bioactmat.2020.03.001.
14. Haas H, Borquez IHE, inventors; BioNTech RNA Pharmaceuticals GmbH, assignee. Stable formulations of lipids and liposomes. US Patent 11,173,120. November 16, 2021.
15. Burdette D, Ci L, Shilliday B, et al. Systemic exposure, metabolism, and elimination of [14C]-labeled amino lipid, lipid 5, after a single administration of mRNA encapsulating lipid nanoparticles to Sprague–Dawley rats. Drug Metab Dispos. 2023;51(7):804–812. https://doi.org/10.1124/dmd.122.001194.
16. Packer M, Gyawali D, Yerabolu R, Schariter J, White P. A novel mechanism for the loss of mRNA activity in lipid nanoparticle delivery systems. Nat Commun. 2021;12(1):6777. https://doi.org/10.1038/s41467-021-26926-0.
17. Blenke EO, Örnskov E, Schöneich C, et al. The storage and in-use stability of mRNA vaccines and therapeutics: Not a cold case. J Pharm Sci. 2023;112(2):386–403. https://doi.org/10.1016/j.xphs.2022.11.001.
18. Kamiya M, Matsumoto M, Yamashita K, et al. Stability study of mRNA–lipid nanoparticles exposed to various conditions based on the evaluation between physicochemical properties and their relation with protein expression ability. Pharmaceutics. 2022;14(11):2357. https://doi.org/10.3390/pharmaceutics14112357.
19. De A, Ko YT. Why mRNA–ionizable LNPs formulations are so short-lived: Causes and way out. Expert Opin Drug Deliv. 2023;20(2):175–187. https://doi.org/10.1080/17425247.2023.2162876.
20. Meulewaeter S, Nuytten G, Cheng MHY, et al. Continuous freeze-drying of messenger RNA lipid nanoparticles enables storage at higher temperatures. J Control Release. 2023;357:149–160. https://doi.org/10.1016/j.jconrel.2023.03.039.
21. Kalita T, Dezfouli SA, Pandey LM, Uludag H. siRNA functionalized lipid nanoparticles (LNPs) in management of diseases. Pharmaceutics. 2022;14(11):2520. https://doi.org/10.3390/pharmaceutics14112520.
22. Pratsinis A, Fan Y, Portmann M, et al. Impact of non-ionizable lipids and phase mixing methods on structural properties of lipid nanoparticle formulations. Int J Pharm. 2023;637:122874. https://doi.org/10.1016/j.ijpharm.2023.122874.
23. Aldosari BN, Alfagih IM, Almurshedi AS. Lipid nanoparticles as delivery systems for RNA-based vaccines. Pharmaceutics. 2021;13(2):206. https://doi.org/10.3390/pharmaceutics13020206.
24. Evers MJW, Kulkarni JA, van der Meel R, Cullis PR, Vader P, Schiffelers RM. State-of-the-art design and rapid-mixing production techniques of lipid nanoparticles for nucleic acid delivery. Small Methods. 2018;2(9):1700375. https://doi.org/10.1002/smtd.201700375.
25. Shi D, Beasock D, Fessler A, et al. To PEGylate or not to PEGylate: Immunological properties of nanomedicine's most popular component, polyethylene glycol and its alternatives. Adv Drug Deliv Rev. 2022;180:114079. https://doi.org/10.1016/j.addr.2021.114079.
26. Senti ME, de Jongh CA, Dijkxhoorn K, et al. Anti-PEG antibodies compromise the integrity of PEGylated lipid-based nanoparticles via complement. J Control Release. 2022;341:475–486. https://doi.org/10.1016/j.jconrel.2021.11.042.
27. Chen W-A, Chang D-Y, Chen B-M, Lin Y-C, Barenholz Y, Roffler SR. Antibodies against poly(ethylene glycol) activate innate immune cells and induce hypersensitivity reactions to PEGylated nanomedicines. ACS Nano. 2023;17(6):5757–5772. https://doi.org/10.1021/acsnano.2c12193.
28. Ibrahim M, Ramadan E, Elsadek NE, et al. Polyethylene glycol (PEG): The nature, immunogenicity, and role in the hypersensitivity of PEGylated products. J Control Release. 2022;351:215–230. https://doi.org/10.1016/j.jconrel.2022.09.031.
29. Kozma GT, Mészáros T, Vashegyi I, et al. Pseudo-anaphylaxis to polyethylene glycol (PEG)-coated liposomes: Roles of anti-PEG IgM and complement activation in a porcine model of human infusion reactions. ACS Nano. 2019;13(8):9315–9324. https://doi.org/10.1021/acsnano.9b03942.
30. Chen B-M, Cheng T-L, Roffler SR. Polyethylene glycol immunogenicity: Theoretical, clinical, and practical aspects of anti-polyethylene glycol antibodies. ACS Nano. 2021;15(9):14022–14048. https://doi.org/10.1021/acsnano.1c05922.
31. Musakhanian J, Rodier J-D, Dave M. Oxidative stability in lipid formulations: A review of the mechanisms, drivers, and inhibitors of oxidation. AAPS PharmSciTech. 2022;23(5):151. https://doi.org/10.1208/s12249-022-02282-0.
32. Herold DA, Keil K, Bruns DE. Oxidation of polyethylene glycols by alcohol dehydrogenase. Biochem Pharmacol. 1989;38(1):73–76. https://doi.org/10.1016/0006-2952(89)90151-2.
33. Nogueira SS, Schlegel A, Maxeiner K, et al. Polysarcosine-functionalized lipid nanoparticles for therapeutic mRNA delivery. ACS Appl Nano Mater. 2020;3(11):10634–10645. https://doi.org/10.1021/acsanm.0c01834.
34. Xenetic Biosciences receives program update from partner Shire's phase 1/2 study evaluating SHP656 in development as a long-acting treatment for hemophilia A. Xenetic Biosciences. Published May 22, 2017. Accessed May 14, 2023. https://www.xeneticbio.com/news-media/press-releases/detail/61/xenetic-biosciences-receives-program-update-from-partner.
35. Han X, Zhang T, Liu M, Song Y, Liu X, Deng Y. Polysialic acid modified liposomes for improving pharmacokinetics and overcoming accelerated blood clearance phenomenon. Coatings. 2020;10(9):834. https://doi.org/10.3390/coatings10090834.
36. Rietwyk S, Peer D. Next-generation lipids in RNA interference therapeutics. ACS Nano. 2017;11(8):7572–7586. https://doi.org/10.1021/acsnano.7b04734.
37. Ndeupen S, Qin Z, Jacobsen S, Bouteau A, Estanbouli H, Igyártó BZ. The mRNA–LNP platform's lipid nanoparticle component used in preclinical vaccine studies is highly inflammatory. iScience. 2021;24(12):103479. https://doi.org/10.1016/j.isci.2021.103479.
38. Swetha K, Kotla NG, Tunki L, et al. Recent advances in the lipid nanoparticle-mediated delivery of mRNA vaccines. Vaccines. 2023;11(3):658. https://doi.org/10.3390/vaccines11030658.
39. Bost JP, Barriga H, Holme MN, et al. Delivery of oligonucleotide therapeutics: Chemical modifications, lipid nanoparticles, and extracellular vesicles. ACS Nano. 2021;15(9):13993–14021. https://doi.org/10.1021/acsnano.1c05099.
40. Herrera M, Kim J, Eygeris Y, Jozic A, Sahay G. Illuminating endosomal escape of polymorphic lipid nanoparticles that boost mRNA delivery. Biomater Sci. 2021;9(12):4289–4300. https://doi.org/10.1039/d0bm01947j.
41. Han X, Zhang H, Butowska K, et al. An ionizable lipid toolbox for mRNA delivery. Nat Commun. 2021;12(1):7233. https://doi.org/10.1038/s41467-021-27493-0.
42. Verbeke R, Hogan MJ, Loré K, Pardi N. Innate immune mechanisms of mRNA vaccines. Immunity. 2022;55(11):1993–2005. https://doi.org/10.1016/j.immuni.2022.10.014.
43. Kumeria T, McInnes SJP, Maher S, Santos A. Porous silicon for drug delivery applications and theranostics: Recent advances, critical review and perspectives. Expert Opin Drug Deliv. 2017;14(12):1407–1422. https://doi.org/10.1080/17425247.2017.1317245.
44. Jurkić LM, Cepanec I, Pavelić SK, Pavelić K. Biological and therapeutic effects of ortho-silicic acid and some ortho-silicic acid-releasing compounds: New perspectives for therapy. Nutr Metab (Lond). 2013;10(1):2. https://doi.org/10.1186/1743-7075-10-2.
45. Da Silva Sanchez AJ, Dobrowolski C, Cristian A, et al. Universal barcoding predicts in vivo ApoE-independent lipid nanoparticle delivery. Nano Lett. 2022;22(12):4822–4830. https://doi.org/10.1021/acs.nanolett.2c01133.
46. Glassman PM, Myerson JW, Ferguson LT, et al. Targeting drug delivery in the vascular system: Focus on endothelium. Adv Drug Deliv Rev. 2020;157:96–117. https://doi.org/10.1016/j.addr.2020.06.013.
47. Verma M, Ozer I, Xie W, Gallagher R, Teixeira A, Choy M. The landscape for lipid-nanoparticle-based genomic medicines. Nat Rev Drug Discov. 2023;22(5):349–350. https://doi.org/10.1038/d41573-023-00002-2.
48. Melamed JR, Yerneni SS, Arral ML, et al. Ionizable lipid nanoparticles deliver mRNA to pancreatic β cells via macrophage-mediated gene transfer. Sci Adv. 2023;9(4):eade1444. https://doi.org/10.1126/sciadv.ade1444.
49. Niculescu A-G, Bîrcă AC, Grumezescu AM. New applications of lipid and polymer-based nanoparticles for nucleic acids delivery. Pharmaceutics. 2021;13(12):2053. https://doi.org/10.3390/pharmaceutics13122053.
50. Huayamares SG, Lokugamage MP, Rab R, et al. High-throughput screens identify a lipid nanoparticle that preferentially delivers mRNA to human tumors in vivo. J Control Release. 2023;357:394–403. https://doi.org/10.1016/j.jconrel.2023.04.005.
51. Maurizi A, Patrizii P, Teti A, et al. Novel hybrid silicon–lipid nanoparticles deliver a siRNA to cure autosomal dominant osteopetrosis in mice. Implications for gene therapy in humans. Mol Ther Nucleic Acids. 2023;33:925–937. https://doi.org/10.1016/j.omtn.2023.08.020.
52. Chen S, Tam YYC, Lin PJC, Sung MMH, Tam YK, Cullis PR. Influence of particle size on the in vivo

potency of lipid nanoparticle formulations of siRNA. J Control Release. 2016;235:236–244. https://doi.org/10.1016/j.jconrel.2016.05.059.
53. Food & Drug Administration. Liposome Drug Products: Chemistry, Manufacturing, and Controls; Human Pharmacokinetics and Bioavailability; and Labeling Documentation; 2018. Docket No. FDA-2016-D-2817. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/liposome-drug-products-chemistry-manufacturing-and-controls-human-pharmacokinetics-and.
54. Hatit MZC, Dobrowolski CN, Lokugamage MP, et al. Nanoparticle stereochemistry-dependent endocytic processing improves in vivo mRNA delivery. Nat Chem. 2023;15(4):508–515. https://doi.org/10.1038/s41557-023-01138-9.
55. Da Silva Sanchez AJ, Zhao K, Huayamares SG, et al. Substituting racemic ionizable lipids with stereopure ionizable lipids can increase mRNA delivery. J Control Release. 2023;353:270–277. https://doi.org/10.1016/j.jconrel.2022.11.037.
56. Chong ZX, Yeap SK, Ho WY. Transfection types, methods and strategies: A technical review. PeerJ. 2021;9:e11165. https://doi.org/10.7717/peerj.11165.
57. Baran-Rachwalska P, Torabi-Pour N, Sutera FM, et al. Topical siRNA delivery to the cornea and anterior eye by hybrid silicon–lipid nanoparticles. J Control Release. 2020;326:192–202. https://doi.org/10.1016/j.jconrel.2020.07.004.
58. Nag K, Sarker MEQ, Kumar S, et al. DoE-derived continuous and robust process for manufacturing of pharmaceutical-grade wide-range LNPs for RNA-vaccine/drug delivery. Sci Rep. 2022;12(1):9394. https://doi.org/10.1038/s41598-022-12100-z.
59. Cameau E, Zhang P, Ip S, Mathiasson L, Stenklo K. Process & analytical insights for GMP manufacturing of mRNA lipid nanoparticles. Cell Gene Ther Insights. 2022;8(4):621–635. https://insights.bio/cell-and-gene-therapy-insights/journal/article/2515/Process-analytical-insights-for-GMP-manufacturing-of-mRNA-lipid-nanoparticles.
60. Catignol P, Lim H. Overcoming bottlenecks in RNA manufacturing. Pharma's Almanac. Published October 24, 2022. Accessed July 2, 2023. https://www.pharmasalmanac.com/articles/overcoming-bottlenecks-in-mrna-manufacturing.
61. Daniel S, Kis Z, Kontoravdi C, Shah N. Quality by design for enabling RNA platform production processes. Trends Biotechnol. 2022; 40(10):1213–1228. https://doi.org/10.1016/j.tibtech.2022.03.012.
62. De A, Ko YT. A tale of nucleic acid–ionizable lipid nanoparticles: Design and manufacturing technology and advancement. Expert Opin Drug Deliv. 2023;20(1):75–91. https://doi.org/10.1080/17425247.2023.2153832.
63. Sahin U, Türeci Ö. Personalized vaccines for cancer immunotherapy. Science. 2018;359(6382):1355–1360. https://doi.org/10.1126/science.aar7112.
64. RNA based therapeutic market update 2023: Projected to cross market value of USD 25.12 billion by 2030. PharmiWeb.com. Updated May 24, 2023. Accessed June 15, 2023. https://www.pharmiweb.com/press-release/2023-05-24/rna-based-therapeutic-market-update-2023-projected-to-cross-market-value-of-usd-2512-billion-by-20.

BIOGRAPHIES

Dr. Suzanne Saffie-Siebert is Founder & CEO, SiSaf Ltd, and the inventor of the company's proprietary Bio-Courier technology platform. She has over 25 years of diversified pharmaceutical industry experience and is one of the pioneers of using drug delivery carriers for nucleic acids. Her previous leadership positions include Director of Research at pSiMedica Ltd (spin out from QinetiQ) and Head of the Drug Delivery Centre at Dompé SpA (Italy). Suzanne earned her PhD from the School of Pharmacy at the University of London and is inventor or co-inventor of numerous drug delivery patents. She also obtained a Business in Bioscience Diploma from Oxford Brookes University Business School.

Dr. Michael Welsh is Chief Scientific Officer, SiSaf Ltd. He is an expert in disease stage and biological models and trained as a virologist and immunologist in human and animal health. Since joining SiSaf in 2014, he has worked on a broad range of pre-clinical and clinical programmes involving Bio-Courier technology. He was previously Head of the Virology Department in a UK Government research institute and obtained his qualifications (first class honours degree and PhD in microbiology) from Queen's University Belfast.

Dr. Nissim Torabi-Pour is Chief Technical Officer, SiSaf Ltd and has played an important role in the development of Bio-Courier technology since the early research phase. Prior to joining SiSaf, he worked as Technical Project Manager and as Project Director at various Biotech companies including pSiMedica Ltd and Global Technologies (NZ) Ltd. His academic research included work on cancer and inflammatory diseases at the Mayo Clinic, USA, and the Royal London Hospital, and on solid and semi-solid drug delivery formulations at Jena University in Germany. Dr. Torabi-Pour earned his PhD at the School of Medicine and Dentistry, University of London.

Dr. Flavia M. Sutera is Head of Preclinical Development, SiSaf Ltd, responsible for the preclinical development of SiSaf's gene therapy pipeline. She has been a key member of SiSaf's R&D team since 2016, leading many of the laboratory activities related to Bio-Courier design and optimization, both in-house and with academic partners. Dr Sutera obtained her PhD in Experimental Medicine and Neuroscience from the University of Palermo, Italy.

CLINICAL TRIALS

Faithful Migration: Shifting Patient Reported Outcomes From Paper to Electronic

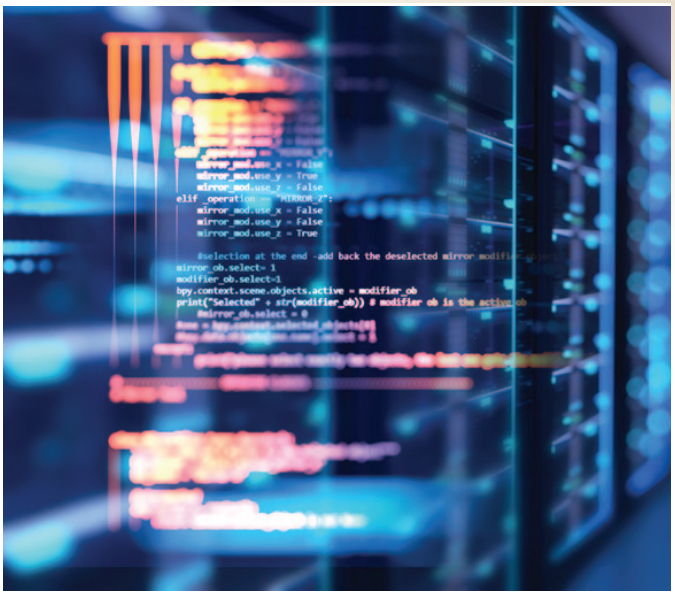
By: Melissa Mooney

INTRODUCTION

Patient reported outcomes (PROs) are one of the four types of clinical outcome assessments (COAs) that play an important role in the evaluation of key study objectives often critical to the success of clinical trials. Most PRO instruments were originally designed to be administered in paper format, but according to recent market research from Industry Standard Research, 89% of respondents now report a preference for using electronic data capture over traditional paper methods. Given this shift, organizations are now focusing on electronic PROs (ePROs).

Not only do participants prefer the electronic method, but implementing ePROs minimizes data loss and errors, as well as increases response rate. However, before an instrument is implemented electronically, it's important that faithful migration is performed. This important step ensures the original properties of the paper PRO remain intact as much as possible when migrating from the existing paper PRO to an ePRO format.

This process needs to be completed very carefully as current guidance requires equivalence when migrating paper PROs to ePROs – essentially ensuring all information shared and question phrasing is of equal meaning, value, and implication in all applications. Faithful migration ensures the content, meaning, and measurement properties of the questionnaire are retained when migrating it from paper to electronic format. However, some modifications may be necessary to align with the electronic modality. The level of modification determines what methodology may be required to demonstrate equivalency. Prior to discussing ways to establish equivalence per modification level, it is best to understand the recommended steps of faithful migration.



FAITHFUL MIGRATION STARTS WITH THESE THREE STEPS

Organizations should closely adhere to the following:

1. Contact the instrument's copyright holder or developer to determine if there are any requirements for an electronic migration, and obtain permission or licensing as needed.

2. Identify any changes that need to be made by reviewing the original version of the instrument. It may be necessary to once again contact the developer or copyright holder to obtain approval for the changes necessary to migrate to the electronic version. Exact words and the order of the questions and responses should be kept where possible. There may be spacing constraints, so evaluation of the instructions and where they are placed, whether that is on the same page or the following page, is necessary. Aesthetic elements should also be incorporated, such as the spacing between questions and responses and font size. The navigation of the ePRO should be

intuitive and indications should be clear on moving forward and backward.

3. Sending screenshots of the ePRO back to the developer or copyright holder for both review and approval may be a required third step.

SUCCESSFULLY ADDRESSING MODIFICATION LEVELS

Within the migration process, there may be modifications necessary to ensure equivalency. There are three distinct types of modifications: minor, moderate, and substantial. Minor modifications are common and not expected to change any meaning or interpretation of questions or responses. A specific example of a minor modification would be updating the phrase Please Circle on a written form to Please Select on an electronic form.

Moderate modifications may have an impact on the patient's ability to interpret and therefore respond to questions. These modifications are typically more format related, such as splitting a question across multiple screens. While minor and moderate changes are mostly related to marking responses or formatting, a substantial modification is most likely to impact the patient's ability to interpret and respond to questions. Things such as removing items or removing recall periods would be considered a substantial modification. More impactful modifications (moderate and substantial) should be avoided, when possible, but when they are unavoidable, it is key to provide evidence of equivalency, especially to regulatory bodies.

EQUIVALENCY TESTING FOR EACH LEVEL OF MODIFICATION

Evidence of equivalency may be required by global authorities if data is to be used in a regulatory setting. FDA guidance dictates that when a PRO used to support labeling claims has been modified, evidence of equivalency is required. For each level of modification previously discussed, there are specific forms of evidence needed. For minor modifications, a "think aloud" approach to interviewing, known as cognitive debriefing, is required. A participant is asked to complete both the original PRO measure and the migrated ePRO measure in the presence of an interviewer while they "think aloud." This means interviewers ask participants to describe the meaning of the questions and responses in their own words. This is a form of a qualitative assessment to determine if the migration has affected the meaning of the questions or responses. Between 5-10 participants in the target population should participate in the cognitive debriefing.

For moderate modifications, a quantitative assessment of the comparability of responses from the original measure to the migrated measure, known as equivalence testing, is necessary. The individuals who are part of this testing complete both the original PRO and the migrated ePRO in random orders. Statistical methods are then used to assess the level of agreement between the two measures.

Substantial modifications require full psychometric testing as the psychometric properties of the measure could change with migration. This testing is required to demonstrate test and re-test reliability, internal consistency, and validity to ensure the ePRO is statistically robust. Usability testing, which examines how well participants understand, navigate, and submit responses through the ePRO measure, is a constant between all three types of modifications. Major difficulties seen during usability testing must be addressed and reassessed through additional usability testing. This loop continues until all the substantial issues are rectified.

Regulators and other health organizations encourage electronic modes of data collection from patients. It assists in minimizing data entry error or missing data and is a convenient method of collection for both patients and sponsors. The migration from paper PROs to ePROs should aim to remain as true to the original measure as possible with minimal modifications when necessary. By following the aforementioned steps to faithful migration, the shift to electronic measures is efficient and reliable, especially as there is an increasing body of evidence showing that when minor changes are made to an original measure, the resulting ePRO is likely to be considered equivalent. ◆

BIOGRAPHY

Melissa Mooney is Director, eCOA Solutions Engineering, eCOA Technologies at IQVIA. She has more than 17 years of experience in the development of eCOA solutions for use in clinical trials. Her area of expertise is eCOA solution design, in which she has supported clients and eCOA vendors in developing robust and usable eCOA software solutions that meet eCOA protocol requirements. She also brings a plethora of experience in eCOA requirement gathering, leading eCOA user acceptance testing, eCOA data management, and business development support.

Contract Manufacturing

AbbVie Contract Manufacturing partners with companies across the globe to develop, scale and manufacture pharmaceutical products and bring them successfully to market. Drawing on more than four decades of success as the manufacturing division of AbbVie, we have the depth of experience and the technical knowledge to navigate issues and deliver the innovative solutions customers need. We are much more than a CMO – we are your partner for success. With foresight, scientific expertise and passion we anticipate the technical and compliance challenges along the entire pharmaceutical development journey through to commercialization. We see the complete picture to deliver our customer's vision. With full access to global state-of the-art facilities and world-class talent, our customers have come to depend on our service and quality to deliver real-world results. For more information, visit AbbVie Contract Manufacturing at **www.abbviecontractmfg.com.**

Specialty CDMO

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

Ascendia® Pharma's expanded state-of-the-art 60,000 sq./ft. R&D and manufac-turing facility provides cGMP manufacturing formulation development, pro-cessing and scale-up along with toxicity and clinical trial materials with com-mercial supply for sterile and non-sterile dosage forms, including ophthalmic, parenteral, topical, and oral. Its facility includes the Netzsch Vakumix for state-of-the-art aseptic processing, and a complete suite of Precision NanoSystems equipment to provide comprehensive lipid nanoparticle manufacturing. For more information, visit Ascendia at **www.ascendiapharma.com.**

Parenteral Delivery Devices

FOR BETTER TREATMENT OF CHRONIC DISEASES. iAcross the healthcare continuum, BD is the industry leader in parenteral delivery devices that help health systems treat chronic diseases. We not only continually advance clinically proven, prefillable drug delivery systems, we do so with a vision to help healthcare providers gain better understanding of how patients self-inject their chronic disease therapies outside the healthcare setting. This is why we partner with leading pharmaceutical and biotech companies worldwide to develop digitally-connected self-injection devices — including wearable injectors and autoinjectors — to capture valuable data that can be shared with caregivers. Discover how BD brings new ideas and solutions to customers, and new ways to help patients be healthy and safe. For more information, visit BD Medical – Pharmaceutical Systems at **bd.com/Discover-BD1.**

Formulation Technology

The scientists at Ligand Pharmaceuticals have developed in-house and aided clients in developing parenteral, oral, ophthalmic, nasal, and inhalation formulations with Captisol and other cyclodextrins. With the recent addition of internal resources and analytical tools, we can provide greater responsiveness for collaborative feasibility and development programs. In addition, the Captisol team have successfully completed or assisted with orphan designations and approvals, preclinical, CMC, and clinical development for ANDA, 505b2, and traditional NDA programs. Our Team is Ready. Are you? Contact us Today! **www.captisol.com.**

Drug Delivery Platform

Celanese corporation is a global leader in the production of differentiated chemistry solutions and specialty materials used in most major industries and consumer applications. With decades of experience in medical and pharmaceutical applications, we have earned our customers' trust us through providing unrivaled service, world-class expertise, and quality that improve product development, enhance manufacturability, and elevate patient experiences. Our VitalDose technology is a drug delivery platform providing controlled release either through local or systemic dosing in an implant or insert dosage form and is compatible with a wide array of drug molecule types. For more information on the VitalDose drug delivery technology, visit **vitaldose.com.**

Differentiated Injectable Delivery

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.**

Enteric Coatings

New platinum standard for enteric coatings: Evonik has created an advanced combination polymer solution for enteric coatings to reduce processing complexity, lower preparation times and save costs. EUDRAGIT® FL 30 D-55 combines the respective benefits of two existing polymers with well-accepted monographs including EUDRAGIT® L 30 D-55: the gold standard for enteric coatings since 1955. Being highly flexible, plasticizer-free and able to be sprayed with a smooth, fast and no-stick process, it is ideal for microparticulates and other dosage forms that require excellent adhesion. As a single product, preparation times can be reduced by up to 70%. With only a thin film able to provide reliable enteric protection, it creates options for higher drug loadings. For more information, contact Evonik at **healthcare@evonik.com.**

Hands-On Formulation Support

GATTEFOSSÉ

With application and R&D Centers in the United States, France, India, and China, the **Gattefossé group** is providing formulation support for oral, topical, transdermal, and other routes of administration. Equipped with state-of-the-art analytical and processing instruments, we stand to assist with your projects at all stages of development, from solubility screening to late-stage formulation and "proof-of-concept" studies. Moreover, we provide extensive regulatory support, sharing toxicological and safety data, and analytical/characterization methods. For more information, visit Gattefossé at **www.gattefosse.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.**

Capsules, Health & Ingredients

Lonza
Capsules & Health Ingredients

Lonza CHI is a preferred global partner to the pharmaceutical, biotech, and nutraceutical markets. Our pioneering Capsugel® capsules and encapsulation technologies help improve speed of development and execution and the match of dosage form performance to ingredients or API application. Our product portfolio and product services for pharmaceutical partners include: Capsules including customizations, Equipment, and Ingredient/API formulation services. We work to prevent illness and promote a healthier world by enabling our customers to deliver new and innovative medicines that help treat a wide range of diseases. We achieve this by combining technological insight, with world class formulation, manufacturing, scientific expertise and process excellence. For more information, visit Lonza CHI at **https://www.capsugel.com/.**

Medical Manufacturing

MEDBIO®
a caplugs partner

Medbio is a medical manufacturing partner like no other, with the broadest spectrum of solutions. From precision custom molding capabilities, full-service contract manufacturing and value-added services to a wide range of standard protective parts and medical packaging, Medbio is the one partner you need. Our in-house team of engineers is dedicated to deliver the most effective solutions to meet your needs. Our multiple state-of-the-art facilities include over 80,000 sq ft of cleanroom manufacturing, including custom built automation cells. We are ISO 13485:2016 certified and FDA registered. Together with sister company Caplugs, one of the world's leading plastic molders, we have worked with over 1,500 medical and biotech customers and look forward to putting our vast expertise to work for you. For more information, visit Medbio at **https://medbiollc.com/.**

Functional Chemicals

MITSUBISHI GAS CHEMICAL

Mitsubishi Gas Chemical (MGC) is a leading company in the field of functional chemicals, such as oxygen barrier and absorbing polymers. MGC established the Advanced Business Development Division in 2015 for tackling a variety of today's problems, and the division created OXYCAPT™ Multilayer Plastic Vial & Syringe to solve some issues of existing primary packaging for injectable drugs. OXYCAPT Vial & Syringe consists of three layers. The inner and outer layers are made of cyclo-olefin polymer (COP), the most reliable polymer in the pharmaceutical industry. The middle layer is made of state-of-the-art polyester developed by MGC. The oxygen-barrier property is almost equivalent to glass and much better than COP. OXYCAPT also provides an ultra violet (UV) barrier. For more information, visit Mitsubishi Gas Chemical at **www.mgc.co.jp/eng/products/abd/oxycapt.html.**

Patient-Focused Delivery Devices

Nemera
we put patients first

As a world-leading drug delivery device solutions provider, **Nemera's** goal of putting patients first enables it to design and manufacture devices that maximize treatment efficacy. Nemera is a holistic partner and helps its customers succeed in the sprint to market with its combination products. From early device strategy to state-of-the-art manufacturing, Nemera is committed to the highest quality standards. Agile and open-minded, the company works with its customers as colleagues. Together, they go the extra mile to fulfil its mission. For more information, visit Nemera at **www.nemera.net.**

High-Quality Reagents

Oakwood Chemical
Enabling Discovery

Oakwood Chemical is a leader in selling high-quality reagents to academic, chemical, and pharmaceutical customers for over 30 years. Located in the South Carolina Lowcountry, we have over 10,000 square feet of laboratory space, as well as two large warehouses totaling 200,000 square feet with over 150,000 chemicals in stock. We offer benchtop to production quantities of inorganic and organic reagents, solvents, salts, catalysts, and biochemicals in numerous grades (reagent, anhydrous, ACS, HPLC, LCMS, NMR, USP) and in different amounts (from lab bench to industrial drum sizes). Let us help you in succeeding in this high growth industry. For more information, visit Oakwood Chemical at **www.oakwoodchemical.com.**

Injectable Drug Delivery

Owen Mumford
Pharmaceutical Services

Owen Mumford Pharmaceutical Services is a specialist in the design, development, and manufacture of injectable drug delivery systems for the pharmaceutical, biotech, and generics industries. These include single-dose and multi-dose reusable and disposable auto-injectors, pens, and syringes for subcutaneous and intramuscular administration. Our innovative products are designed to meet both the need of our pharmaceutical partners and their patients by facilitating ease of use and improving safety and patient compliance. Our devices are also designed with the aim of reducing complexity and risk for the pharmaceutical and biotech industry in the development of their combination products. Our products are supported by our services, and we work with our partners every step of the way, supporting and guiding from initial concept stage through to taking the solution to market. For more information, visit Owen Mumford Pharmaceutical Services at **www.ompharmaservices.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.**

Plastics Processing & Development

WIRTHWEIN
MEDICAL

Founded in 1946, **Wirthwein Medical GmbH & Co. KG** is today a high-performance system supplier in plastics processing and a development partner for plastic-based and customer-specific product solutions. Focusing on quality and innovation, Wirthwein Medical has also internationally made its mark in the diagnostics, medical technology, pharmaceutics industries – with high-precision, components, packaging, and systems. In addition, proprietary products in the pharmaceutical sector complement the product portfolio. For more information, visit Wirthwein Medical GmbH & Co. at **www.wirthwein-medical.com.**

September 2024 Advertiser Index

COMPANY	PAGE	CONTACT	WEBSITE
AbbVie Contract Manufacturing	2	abbviecontractmfg@abbvie.com	abbviecontractmfg.com
Adare Pharmaceuticals	76	BusDev@adareps.com	AdarePharmaSolutions.com
Ascendia Pharma	7	bd@ascendiapharma.com	www.ascendiapharma.com
Captisol	3	(858) 550-5632	www.captisol.com
Celanese	9	healthcare@celanese.com	www.vitaldose.com
Credence MedSystems	23	info@CredenceMed.com	www.CredenceMed.com
Drug Development & Delivery	4, 51	info@drug-dev.com	www.drug-dev.com
Evonik	14	healthcare@evonik.com	evonik.com/healthcare
Gerresheimer	19	info@gerresheimer.com	www.gerresheimer.com
Oakwood Chemical, Inc.	13	sales@oakwoodchemical.com	www.oakwoodchemical.com
Owen Mumford Pharmaceutical Services	5	pharmaservices@owenmumford.com	www.ompharmaservices.com
MedBio	15	info@medbiollc.com	https://medbiollc.com/
Mitsubishi	17	+81 3 3283 4913	https://www.mgc.co.jp/eng/products/abd/oxycapt.html
PharmaCircle	30-31	contact@pharmacircle.com	www.pharmacircle.com
Wirthwein Medical	11	info@wirthwein-medical.com	www.wirthwein-medical.com

YOUR PARTNER FOR SMALL MOLECULE ORAL SOLID DOSE SUCCESS

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.

Visit us at CPHI Milan | Stand #5A33

TRANSFORMING DRUG DELIVERY. TRANSFORMING LIVES.

ADARE®
PHARMA SOLUTIONS

ADAREPHARMASOLUTIONS.COM