Drug Development & Delivery

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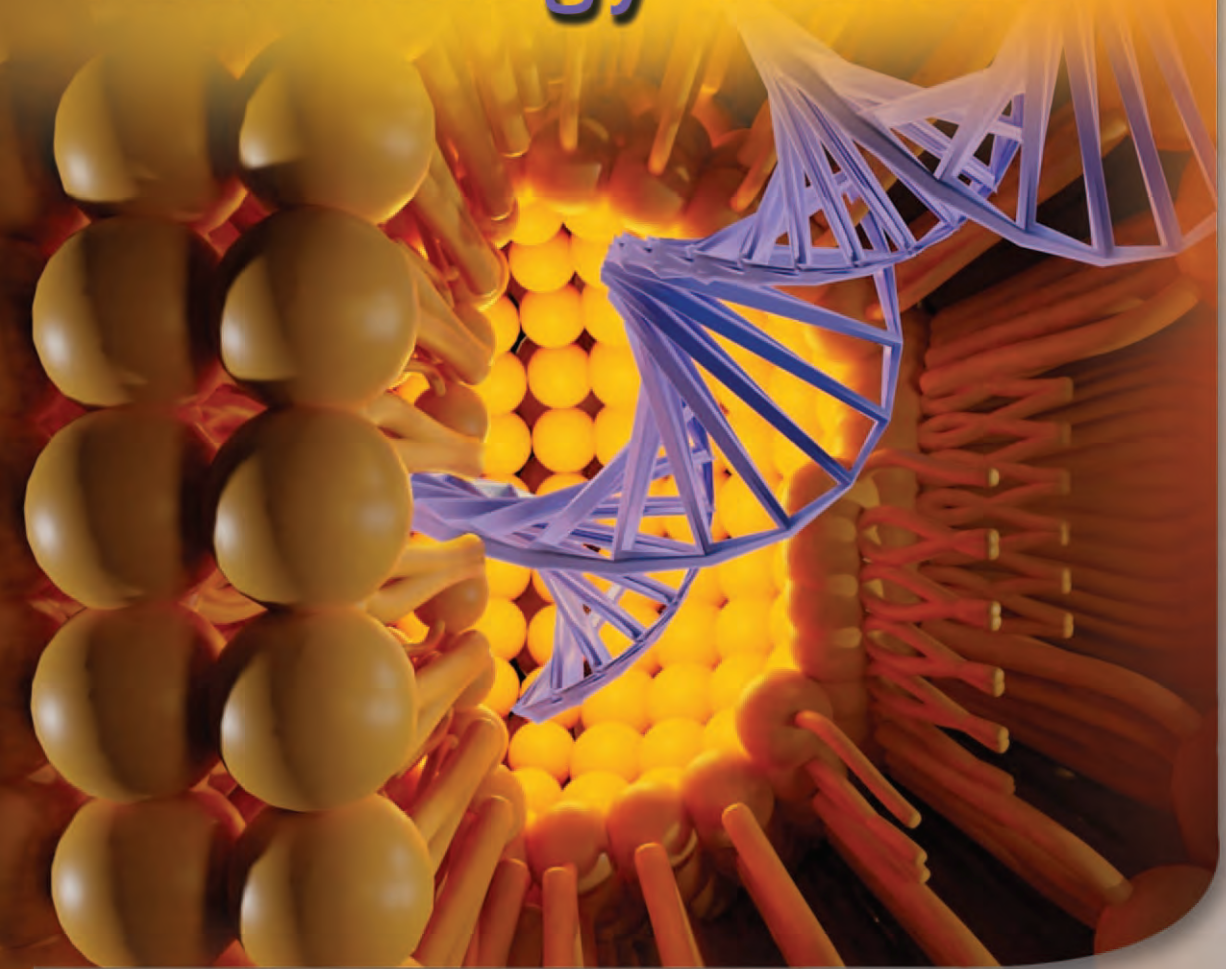

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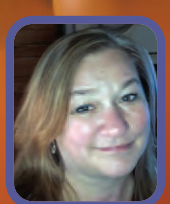

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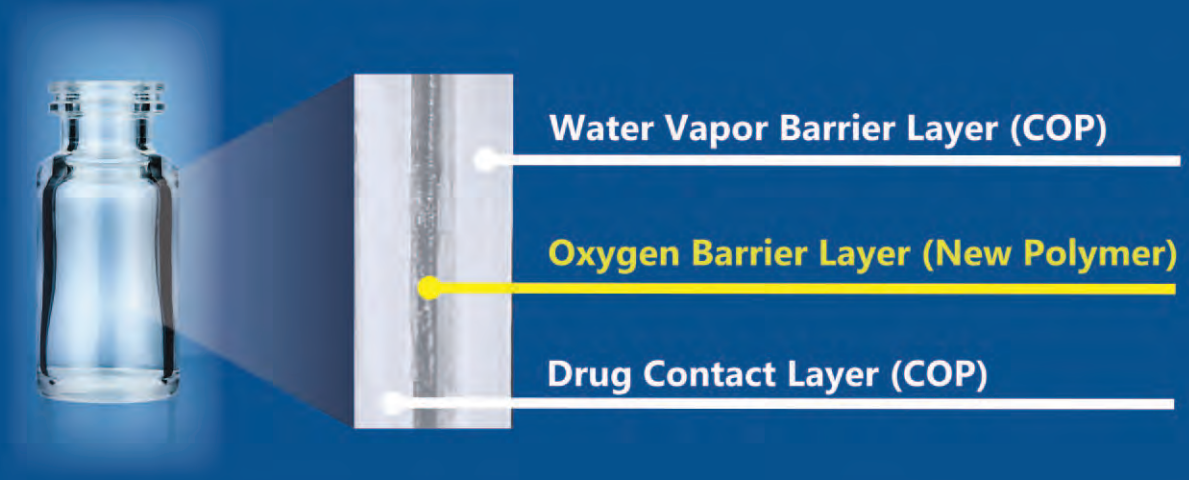

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Lipid Nanoparticle Platform Technology

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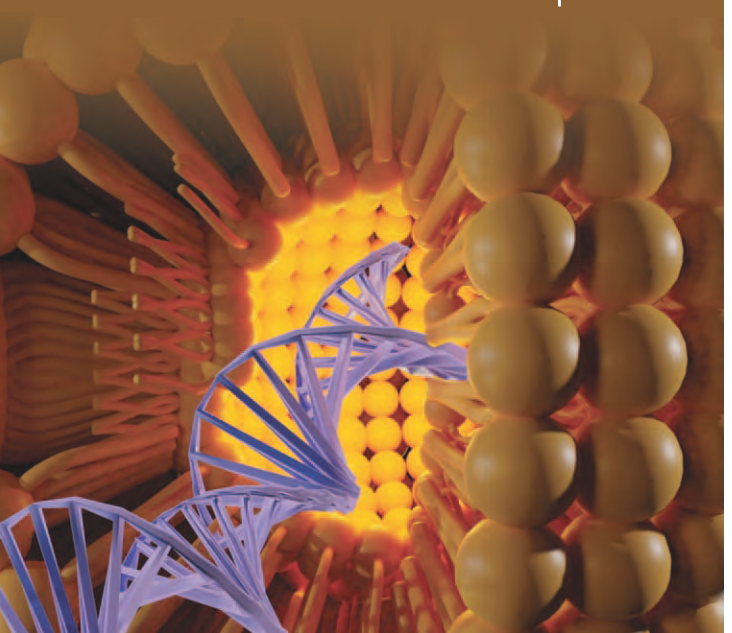
p.22



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A Dose of AI

"Elon Musk just warned the world that Artificial Intelligence (AI) is dangerous and has the potential to destroy civilization. Yet, AI will likely be used in nearly every industry, and the biopharma industry is no exception. A new report from VisionGain shows that 75% of pharmaceutical organizations want to use automated solutions more frequently, driven by injectable drug delivery."

p.46

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Radiant Biotherapeutics Emerges From Stealth Mode With $8-Million Seed Round & Two Pharma Partnerships

Radiant Biotherapeutics emerged from stealth mode unveiling an $8-million seed financing and two significant pharmaceutical partnerships. The company, based on foundational IP from the labs of Dr. Jean-Philippe Julien at The Hospital for Sick Children (SickKids) and Dr. Bebhinn Treanor at the University of Toronto, was created by Amplitude Venturesc which also led the seed round along with launch partner, SickKids and additional investors Alexandria Investments, FACITc and Toronto Innovation Acceleration Partners (TIAP).

"This financing enables us to advance and validate our Multabody platform among several oncology programs with potential best-in-class profiles," said Arthur J. Fratamico, President and Chief Executive Officer of Radiant. "We are maximizing the potential of the Multabody platform by building a pipeline of candidates in our therapeutic areas of focus and pursuing additional research collaborations outside of those areas. The interest we received from potential partners to date is significant, resulting in two undisclosed collaborations with global pharma partners."

Radiant's Multabody platform exploits avidity – stronger binding power – coupled with multi-specificity to deliver highly efficacious antibodies with exceptional potency extending beyond today's antibody technologies to overcome the limitations of current approaches. This innovative platform has demonstrated the potential to deliver a new class of multi-functional biologics to tackle complex and diverse diseases, including cancer, autoimmune conditions and infectious diseases. Built on an antibody framework, the Multabody retains monoclonal antibody-like developability and pharmacokinetics, creating a truly superior next-generation therapeutic.

"Radiant's first-of-its-kind Multabody platform has the potential to transform antibody therapeutics," said Bharat Srinivasa, founding CEO and Principal at Amplitude Ventures. "The Radiant team is showcasing their ability to rapidly develop Multabodies – from concept to in vivo POC within six months while demonstrating superior potency and efficacy to current antibodies and leveraging existing manufacturing processes.

This proprietary platform has exciting potential to also create unique therapies targeting biological pathways not amenable to current antibody approaches."

Radiant Biotherapeutics is a revolutionary antibody platform company leading the new frontier of multi-valent, multi-specific therapeutics to deliver transformative therapies for patients. The proprietary Multabody platform leverages avidity and multi-specificity simultaneously, to generate highly efficacious Multabodies with superior potency than other antibody platforms. These powerful Multabodies have potential to deliver a new class of biologics to tackle complex, heterogenous diseases, such as cancer, that often have challenging targets and mechanisms. Multabody production and manufacturing is flexible, modular and scalable, and leverages standard antibody CMC processes. The groundbreaking efficiency of the platform is driving a novel pipeline of mono, bi- and tri-specific biologics in multiple therapeutics areas. Strategic partnerships with two leading biopharmaceutical companies validate the platform and its broad scientific and clinical utility.

Founded in 1827, the University of Toronto is Canada's leading institution of learning, discovery and knowledge. U of T is one of the world's leading research-intensive universities, driven to invent and innovate. It is also one of the top five universities in the world for startup incubator programs. In the last 10 years, the U of T entrepreneurship community has created more than 600 companies and raised over $2.5 billion in investment capital.

Arrowhead Pharmaceuticals' Proprietary Pulmonary TRiM Platform Achieves High Levels of Target Gene Knockdown & Long Duration of Effect

Arrowhead Pharmaceuticals Inc. recently announced interim results from an ongoing Phase 1/2 clinical study of ARO-RAGE, the company's investigational RNA interference (RNAi) therapeutic designed to reduce production of the receptor for advanced glycation end products (RAGE) as a potential treatment for inflammatory pulmonary diseases, such as asthma. These data represent the first clinical demonstration of the potential utility of Arrowhead's proprietary Targeted RNAi Molecule (TRiM) platform optimized for delivery to the lungs.

Matthias Salathe, MD, Professor, Pulmonary, Critical Care and Sleep Medicine, and Vice Chancellor for Research at the University of Kansas Medical Center, said "These interim ARO-RAGE Phase 1/2 data are highly encouraging. Unmet need continues to exist for many patients with severe asthma who suffer from persistent symptoms and exacerbations, despite current therapies. Reducing expression of the RAGE protein in pulmonary epithelial cells to the degree that ARO-RAGE has demonstrated to date in this study has the potential to treat patients with asthma and other inflammatory lung diseases in a fundamentally new way. RAGE represents a promising target for intervention as its activation has been implicated as a proximal regulator of the inflammatory cascade in the asthmatic airway, and thus RAGE silencing may result in potent anti-inflammatory effects. I look forward to the availability of additional results from this important trial."

Christopher Anzalone, PhD, President and CEO at Arrowhead, said "We think these interim data with ARO-RAGE represent clinical validation of Arrowhead's inhaled pulmonary TRiM platform and, specifically, of ARO-RAGE as a potential new therapy to treat patients with inflammatory lung diseases. The high level of target gene knockdown, the long duration of effect, and the promising safety and tolerability results are all very encouraging signs for our growing pipeline of RNAi therapeutic candidates that leverage this same platform. We look forward to providing additional data at our upcoming R&D Day on June 1, 2023, and at future medical meetings."

ARORAGE-1001 (NCT05276570) is a Phase 1/2a, randomized, double-blinded, placebo-controlled study in normal healthy volunteers (NHV), Part 1, and patients with mild-to-moderate asthma, Part 2. The single ascending dose portion of the study includes 5 sequentially enrolled NHV cohorts with escalating single-dose levels. The multiple ascending dose portion of the study includes 5 NHV cohorts and 3 asthma patient cohorts. The objectives of the study include the assessment of safety and tolerability, pharmacokinetics, and pharmacodynamics of ARO-RAGE in NHVs and patients with asthma.

RAGE is implicated in the pathogenesis of numerous inflammatory diseases, including asthma. Reduction of RAGE expression via RNAi is designed to reduce the amount of RAGE protein expressed on pulmonary epithelial cells. Reduced RAGE expression in the pulmonary epithelium may result in reduction of RAGE-dependent inflammatory pathways, leading to decreased exacerbation frequency and improved airflow in patients with asthma.

NewAmsterdam Pharma Completes Enrollment in Pivotal Phase 3 Trial Evaluating Obicetrapib in Patients With Heterozygous Familial Hypercholesterolemia

NewAmsterdam Pharma Company N.V. announced the completion of patient enrollment in the pivotal Phase 3 BROOKYLN clinical trial evaluating obicetrapib in adult patients with heterozygous familial hypercholesterolemia (HeFH), whose low-density lipoprotein cholesterol (LDL-C) is not adequately controlled, despite being on maximally tolerated lipid-lowering therapy. NewAmsterdam expects to report topline results in the second half of 2024.

The double-blind, placebo-controlled Phase 3 BROOKLYN trial enrolled 354 patients with a history of HeFH across ten countries in North America, Europe, and Africa. The mean baseline LDL-C for enrolled patients is >120 mg/dL despite high intensity statin use reported by approximately 70% of patients during screening. Females comprise approximately 53% of the study population and the median age of participants at baseline is 57 years. Patients were randomized to receive placebo or 10 mg obicetrapib dosed as a once-daily oral treatment with or without food for 52 weeks. The primary objective is to evaluate the effect of obicetrapib on LDL-C levels. Secondary objectives include evaluating the effect of obicetrapib on non-high-density lipoprotein cholesterol (non-HDL-C), apolipoprotein B (ApoB), and lipoprotein (a). The trial is also evaluating the safety and tolerability profile of obicetrapib.

Obicetrapib is a next-generation, oral, low-dose CETP inhibitor that NewAmsterdam is developing to potentially overcome the limitations of current LDL-lowering treatments. The company believes obicetrapib has the potential to be a once-daily oral CETP inhibitor for lowering LDL-C, if approved. In the company's Phase 2b ROSE trial, obicetrapib demonstrated a 51% lowering of LDL-C from baseline at a 10 mg dose level on top of high-intensity statins and, in the Company's Phase 2 ROSE2 trial, the combination of a 10 mg dose of obicetrapib and a 10 mg dose of ezetimibe demonstrated a 59% lowering of LDL-C from baseline. In all three of the company's Phase 2 trials, TULIP, ROSE, and OCEAN, evaluating obicetrapib as a monotherapy or a combination therapy, the company observed statistically significant LDL-lowering activity combined with generally moderate side effects and no drug-related, treatment-emergent serious adverse events. Obicetrapib has demonstrated strong tolerability in more than 600 patients with low or elevated lipid levels (dyslipidemia) in NewAmsterdam's clinical trials to date. The company is conducting two Phase 3 pivotal trials, BROADWAY and BROOKLYN, to evaluate obicetrapib as a monotherapy used as an adjunct to maximally tolerated lipid-lowering therapies to potentially enhance LDL-lowering for high-risk CVD patients. The company began enrolling patients in BROADWAY in January 2022 and in BROOKLYN in July 2022. The company also commenced our Phase 3 PREVAIL CVOT in March 2022, which is designed to assess the potential of obicetrapib to reduce occurrences of MACE, including cardiovascular death, non-fatal myocardial infarction, non-fatal stroke and non-elective coronary revascularization.

Merck Strengthens Immunology Pipeline With Acquisition of Prometheus Biosciences

Merck and Prometheus Biosciences, Inc. recently announced the companies have entered into a definitive agreement under which Merck, through a subsidiary, has agreed to acquire Prometheus for $200.00 per share in cash for a total equity value of approximately $10.8 billion.

"At Merck, we are committed to delivering on our purpose to save and improve lives and continue to identify and secure opportunities where compelling science and value creation align," said Robert M. Davis, Chairman and Chief Executive Officer, Merck. "The agreement with Prometheus will accelerate our growing presence in immunology where there remains substantial unmet patient need. This transaction adds diversity to our overall portfolio and is an important building block as we strengthen the sustainable innovation engine that will drive our growth well into the next decade."

Prometheus is a clinical-stage biotechnology company pioneering a precision medicine approach for the discovery, development, and commercialization of novel therapeutic and companion diagnostic products for the treatment of immune-mediated diseases. The company's lead candidate, PRA023, is a humanized monoclonal antibody (mAb) directed to tumor necrosis factor (TNF)-like ligand 1A (TL1A), a target associated with both intestinal inflammation and fibrosis.

"Prometheus was established to revolutionize the treatment of immune-mediated diseases through the application of a powerful precision medicine approach," said Mark McKenna, Chairman and Chief Executive Officer of Prometheus Biosciences. "This agreement with Merck, a leader in biopharmaceutical research and development, allows Prometheus to maximize the potential for PRA023, while continuing to apply our technology and expertise to fuel further discoveries to address the needs of patients with immune disorders."

Prometheus is developing PRA023 for the treatment of immune-mediated diseases including ulcerative colitis (UC), Crohn's disease (CD), and other autoimmune conditions. In December 2022, the company announced positive results for PRA023 from ARTEMIS-UC, a Phase 2, placebo controlled, study evaluating safety and efficacy in patients with moderate to severely active UC and APOLLO-CD a Phase 2A, open-label, study evaluating safety and efficacy in patients with moderate to severe CD. The findings were recently presented at the 18th Congress of European Crohn's and Colitis Organisation (ECCO).

"By applying a portfolio of powerful analytic tools to a comprehensive collection of IBD samples, Prometheus identified important disease insights that have now yielded a promising late-stage candidate," said Dr. Dean Y. Li, President, Merck Research Laboratories. "I look forward to working with the talented Prometheus team to establish a new paradigm of precision treatment for immune diseases."

Under the terms of the acquisition agreement, Merck, through a subsidiary, will acquire all of the outstanding shares of Prometheus. The acquisition is subject to Prometheus Biosciences shareholder approval. The closing of the proposed transaction will be subject to certain conditions, including the expiration of the waiting period under the Hart-Scott-Rodino Antitrust Improvements Act and other customary conditions. The transaction is expected to close in the third quarter of 2023.

PRA023 is a humanized monoclonal antibody directed to tumor necrosis factor (TNF)-like ligand 1A (TL1A). PRA023 binds both soluble and membrane associated human TL1A with high affinity and specificity. Prometheus is developing PRA023 for the treatment of immune-mediated diseases including UC, CD, and other autoimmune conditions.

Roquette Cuts Ribbon on $25-Million Pharmaceutical Innovation Center in the US

Roquette recently celebrated the grand opening of its new Pharmaceutical Innovation Center, located near Philadelphia, PA, right in the heart of the United States' Northeastern pharmaceutical corridor. Staffed with a team of highly skilled research, application and formulation experts, the new $25-million center will be an advanced training and collaboration hub for pharmaceutical and nutraceutical manufacturers around the world. With a focus on optimizing patient experience with next-generation oral dosage forms, the US facility complements the cutting-edge research activities of Roquette's existing pharma innovation centers in France and Singapore.

Paul Smaltz, Vice President of Pharmaceutical Solutions at Roquette, said "Today's grand opening feels like the start of something special for Roquette. With its strategic location in one of the world's top pharma-producing regions, the new site will unlock even greater opportunities for closer collaboration with our customers in the US and provide a beacon of best practice training and advice to our teams across the globe."

Similar to Roquette's other Innovation Centers, the new US facility is dedicated to furthering the field of pharmaceutical science through cross-industry collaboration, research-led product development and a drive to improve patients' lives. Expert training, troubleshooting and scale-up advice will be priorities at the facility. Planned topics for the first wave of training workshops include selecting excipients for controlled release dosage forms, enhancing bioavailability, and formulating effective orally dispersible and chewable tablets. In addition to formulation-focused sessions, the Innovation Center will host manufacturing-oriented seminars, such as improving wet/dry granulation processes and strategies for effective continuous manufacturing.

Underpinning these training sessions and the center's primary research projects is a suite of the latest pharmaceutical processing, testing and manufacturing equipment. Roquette's customers and partners can harness cutting-edge technologies such as a state-of-the-art R&D continuous manufacturing simulator, compaction simulator, hot-melt extruder, advanced dissolution and particle size testing (laser diffraction), thermal gravimetric analysis (TGA) and modulated differential scanning calorimetry (mDSC) to refine and improve formulations. The site is also fully stocked with brand-new granulation, blending and coating equipment, alongside high-performance liquid chromatography (HPLC) analysis capabilities.

"Our team at the new US Innovation Center has one overarching mission: to foster a seamless connection between cutting-edge science and the practicalities of drug development," said Dr. Tuliani. "Together with Dr. Peter Freed, our newly appointed Head of Global Pharma Customer Technical Support (CTS), we will push the boundaries of pharmaceutical science through close collaborations with leading universities and research institutes, and bring blue sky concepts back to earth for our customers by harnessing decades of prototyping, testing, sales and marketing experience. I am delighted to be joining the Roquette Pharma Solutions team at such an exciting time of innovation and expansion. Today's opening of the US Innovation Center is only the beginning – with our unwavering commitment to serving customers, patients and the scientific community, there is truly no limit to what we can achieve. Watch this space!"

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PCI Pharma Services Announces New Sterile Fill-Finish Capabilities Now Available in Melbourne & San Diego

PCI Pharma Services (PCI), a leading global contract development and manufacturing organization (CDMO), recently announced three new state-of-the-art automated sterile fill-finish machines at its San Diego and Melbourne facilities are now fully operational. The innovative machinery from Cytiva can be used to fill various sterile medications into vials and syringes for small-to-mid scale client needs. The equipment, paired with PCI's end-to-end services, accelerates Speed to Study, and significantly decreases the average turnaround time from proposal signing to the injectable product's distribution.

"As the capacity for CDMOs worldwide to take on new projects shrinks, we're excited to be able to offer integrated sterile fill-finish capabilities, alongside our clinical packaging facilities, to new and existing clients in Melbourne and San Diego," said Brad Payne, Chief Operating Officer, PCI Pharma Services. "Our increased capacity, stockpile of standardized components, including glass, and technical expertise means we can start running batches as soon as needed. This will cut down on the wait times many pharmaceutical companies are facing and begin to help alleviate the global capacity shortage for sterile drug product and downstream packaging."

The Microcell Vial Filler and SA25 Aseptic Filling Workcell at PCI's San Diego facility ensures the delivery of medicines from phase I through phase III, supporting local and global Clinical client needs. Additionally, a Microcell Vial Filler at Melbourne further enhances the early-stage services offered and brings additional capacity to Australia – the world's leading Phase I environment. These advanced machines expedite the filling process with automation and remove the need for human intervention in a sterile environment, creating compliance advantages over standard equipment.

"There are less barriers to entry to start a clinical trial in Australia, as well as significant cost benefits, and with Melbourne being an especially popular place to conduct phase I trials, we knew we needed to bring this capability and added capacity to the local market," said Tim Roberts, Chief Commercial Officer, PCI Pharma Services. "In addition, we are then able to take our clients through their lifecycle journeys with the expansions and advanced capabilities in our New Hampshire and Madison campuses. With successful recent inspections at our Bedford facility by the Brazilian (ANVISA) and Japanese (PDMA) regulatory authorities, our global reach to supply life-changing therapies to patients quickly and safely is wider than before."

To better support its clients throughout the world, PCI has also recently invested in expansions in Rockford, IL, and Tredegar, Wales, as well as established new facilities in Bedford, NH, and Bridgewater, MA.

PCI is a leading global CDMO, providing clients with integrated end-to-end drug development, manufacturing, and packaging capabilities that increase their products' speed to market and opportunities for commercial success. PCI brings proven experience that comes with more than 50 successful product launches each year and over 5 decades in the healthcare services business.

Tiziana Life Sciences Initiates Program to Develop Intranasal Foralumab in Type 1 Diabetes

Tiziana Life Sciences Ltd. recently announced it is initiating a program to develop intranasal foralumab for the treatment or prevention of Type 1 diabetes.

"With the FDA approval of the humanized anti-CD3 mAb TZIELD (teplizumab-mzwv injection) and then its subsequent announced acquisition of Provention Bio by Sanofi for $2.9 billion, CD3 has emerged as an established and attractive target for Type 1 diabetes," said Gabriele Cerrone, Executive Chairman, Founder and interim Chief Executive Officer of Tiziana. "We believed that having a fully human CD3 antibody may offer benefits to patients across many different chronic disease indications."

"The potential of not requiring an injection or infusion and having a take-home self-administered nasally delivered therapy would offer additional benefit and convenience to sufferers of Type 1 diabetes", added Matthew W. Davis, MD, RPh, Chief Medical Officer of Tiziana. "Although given intranasally, our fully human anti-CD3 mAb foralumab has shown to release anti-inflammatory T regulatory cells throughout the body while returning pro-inflammatory effector T cells to their naïve state. We are actively discussing various study designs with our Key Opinion Leaders as well as with an internationally known network of dedicated diabetes physicians. I believe that the data published in PNAS shows that the novel immunomodulatory effects of our intranasal fully human anti-CD3 mAb foralumab may have an important role in the diabetes market."

Activated T cells play an important role in the inflammatory process. Foralumab, the only fully human anti-CD3 monoclonal antibody (mAb), binds to the T cell receptor and dampens inflammation by modulating T cell function, thereby suppressing effector features in multiple immune cell subsets. This effect has been demonstrated in patients with COVID and with multiple sclerosis, as well as in healthy normal subjects. Intranasal foralumab Phase 2 trials are expected to start in the third quarter of 2023 in patients with non-active SPMS. Immunomodulation by nasal anti-CD3 mAb represents a novel avenue for treatment of inflammatory human diseases.

Tiziana Life Sciences is a clinical-stage biopharmaceutical company developing breakthrough therapies using transformational drug delivery technologies to enable alternative routes of immunotherapy. Tiziana's innovative nasal approach has the potential to provide an improvement in efficacy as well as safety and tolerability compared to intravenous (IV) delivery. Tiziana's lead candidate, intranasal foralumab, which is the only fully human anti-CD3 mAb, has demonstrated a favorable safety profile and clinical response in patients in studies to date. Tiziana's technology for alternative routes of immunotherapy has been patented with several applications pending and is expected to allow for broad pipeline applications.

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ProBioGen & ImmunOs Therapeutics Team Up to Deliver Innovative Therapy for Cancer Patients

ProBioGen and ImmunOs Therapeutics recently announcd the extension of their partnership for further large-scale manufacturing of clinical material for IOS-1002, ImmunOs' lead program for the treatment of cancer. ProBioGen previously developed the cell line and the manufacturing process and provided the initial clinical material for ImmunOs' innovative biologic.

"We at ImmunOs are very satisfied with the work done by ProBioGen. We highly appreciate the collaborative partnership with ProBioGen and the team's dedication and solution orientation. The tireless effort of the ProBioGen team has enabled ImmunOs to start clinical development as planned and to meet our milestones," said Jeff Abbey, Chief Operating Officer of ImmunOs Therapeutics.

"Partnership is one of our core values, as it is key in working successfully together. With this in mind we are confident that our continuous collaboration is based on mutual trust and reliability," added Dr. René Brecht, Chief Operations Officer of ProBioGen.

ImmunOs Therapeutics leverages its HLA-based technology platform to develop first-in-class therapeutics for the treatment of cancer and autoimmune diseases. The company has identified specific HLA molecules known to activate the immune system and is utilizing these HLA molecules as the backbone of novel therapies capable of stimulating both the innate and the adaptive immune systems of cancer patients to eliminate tumor cells. ImmunOs' lead program is a multi-functional fusion protein that blocks specific LILRB (leukocyte immunoglobulin-like) and KIR (killer cell immunoglobulin-like) receptors and activates anti-tumor responses. ImmunOs is also developing antibodies to block the activation of specific HLA protein molecules associated with autoimmune diseases.

ProBioGen is a Berlin-based specialist for developing and manufacturing biopharmaceutical active ingredients,

viral vectors and vaccines with applying proprietary technologies to improve product quality and features.

Combining both state-of-the-art development services, based on ProBioGen's CHO.RiGHT expression and manufacturing platform, together with intelligent product-specific technologies yields biologics with optimized properties. Rapid and integrated cell line and process development, comprehensive analytical development and following reliable GMP manufacturing is performed by a highly skilled and experienced team. All services and technologies are embedded in a total quality management system to assure compliance with international ISO and GMP standards (EMA/FDA).

ProBioGen has been operational for more than 25 years. At three locations in Berlin, over 300 employees contribute to the creation of new therapies in medicine and groundbreaking innovations worldwide through their creative and meticulous work. ProBioGen's growth strategy is driven by the expansion of the service value chain through organic growth and potential acquisition. Diversification is a complement driver, while the focus is strict on enabling the development of biopharmaceuticals for tomorrow.

Enlivex Announces Clinical Collaboration to Evaluate Combinations of Allocetra & PD-1 Inhibitor Tislelizumab for Patients With Solid Tumors

Enlivex Therapeutics Ltd. recently announced a clinical collaboration with BeiGene to evaluate the safety and efficacy of Allocetra, an investigational macrophage-reprogramming cell therapy, in combination with tislelizumab, an anti-PD-1 immune checkpoint inhibitor, for the treatment of patients with advanced-stage solid tumors.

"We are excited to explore the potential of Allocetra in combination with tislelizumab, a potentially differentiated PD-1 inhibitor," said Shai Novik, Executive Chairman of Enlivex. "We look forward to integrating tislelizumab into our ongoing Phase 1/2 clinical trial."

"Combinatorial approaches for fighting difficult-to-treat cancers historically have proven to be important in the delivery of better treatments to patients", said Oren Hershkovitz, PhD, CEO of Enlivex. "We believe that the preclinical data observed to date for Allocetra, with its unique macrophage-modulation properties, and immune checkpoints, support the evaluation of the combination for the treatment of patients with the tislelizumab-Allocetra combinations."

Under the terms of the clinical collaboration agreement, Enlivex has agreed to amend its ongoing Phase 1/2 trial in patients with advanced-stage solid tumors to include evaluation of Allocetra in combination with tislelizumab. The Phase 1/2 trial is a multicenter, open-label, dose escalation trial that is expected to enroll up to 48 patients with advanced solid tumors across two trial stages. Stage 1 of the trial will examine escalating doses of Allocetra monotherapy administered intravenously (IV) or intraperitoneally (IP) once a week for three consecutive weeks. Stage 2 will evaluate escalating doses of Allocetra administered IV or IP and combined with anti-PD1 therapy. BeiGene will provide the clinical supply of tislelizumab for the trial.

Tislelizumab (BGB-A317) is a humanized IgG4 anti–PD-1 monoclonal antibody specifically designed to minimize binding to FcγR on macrophages. In pre-clinical studies, binding to FcγR on macrophages has been shown to compromise the anti-tumor activity of PD-1 antibodies through activation of antibody-dependent macrophage-mediated killing of T effector cells. Tislelizumab is being developed as a monotherapy and in combination with other therapies for the treatment of a broad array of both solid tumor and hematologic cancers.

Allocetra is being developed as a universal, off-the-shelf cell therapy designed to reprogram macrophages into their homeostatic state. Diseases such as solid cancers, sepsis, and many others reprogram macrophages out of their homeostatic state. These non-homeostatic macrophages contribute significantly to the severity of the respective diseases. By restoring macrophage homeostasis, Allocetra has the potential to provide a novel immunotherapeutic mechanism of action for life-threatening clinical indications that are defined as "unmet medical needs", as a stand-alone therapy or in combination with leading therapeutic agents.

Enlivex is a clinical-stage macrophage reprogramming immunotherapy company developing Allocetra, a universal, off-the-shelf cell therapy designed to reprogram macrophages into their homeostatic state. Resetting non-homeostatic macrophages into their homeostatic state is critical for immune system rebalancing and resolution of life-threatening conditions.

Absci Partners With Bioinformatics Company M2GEN to Accelerate Drug Creation for Oncology

Absci Corporation and M2GEN recently announced a partnership to create new cancer medicines and bring them to market at unprecedented speed. Absci's generative AI drug creation platform will tap into M2GEN's clinical and molecular data set, ORIEN AVATAR (AVATAR), to accelerate the creation of therapeutics for a range of malignancies and patient profiles, bringing AI drug creation to the fight against cancer.

A key challenge in creating effective cancer treatments is finding specific antigens that can be targeted by immunotherapies. M2GEN's AVATAR database represents a valuable resource for discovering such antigens. Absci will use its reverse immunology technology to first search the database for antibodies from patients with exceptional immune responses, then computationally re-assemble antigen-antibody pairs as promising starting points for drug development.

This partnership brings together AI drug creation technology and oncology bioinformatics to potentially reduce the time and cost to create better cancer treatments. Absci's Integrated Drug Creation platform unites generative AI and wet-lab capabilities to screen billions of cells per week, allowing it to go from AI-designed antibodies to lab-validated candidates in as little as 6 weeks. As the nexus between patients, researchers, and the pharmaceutical industry, M2GEN is uniquely positioned and equipped with the richest clinicogenomic data set, and a lifetime patient-consented Total Cancer Care (TCC) protocol, to accelerate drug discovery and development and transform how cancer is treated. M2GEN's real-world data set comes from its Oncology Research Information Exchange Network (ORIEN) partners, an alliance of 18 cancer centers across more than a dozen US states.

"M2GEN and its ORIEN partners are premier leaders in the field of oncology data research and bring a wealth of unique data sets to our generative AI platform that may enable us to ultimately shave years off the drug discovery process," said Sean McClain, CEO of Absci. "This is an important leap forward to better understand individualized protein-protein interactions on cancer cells, moving us toward delivering on the promise of personalized medicine."

The cornerstone of ORIEN is the lifetime-consented TCC protocol, one of the first longitudinal cancer patient databases of its kind, with over 360,000 patients enrolled nationwide. TCC enables patient monitoring throughout their treatment journey, with the goal to transform how cancer is treated. M2GEN and ORIEN research-facilitated projects are monitored by a multi-institution governing body, which includes scientists and research leaders from network members, to ensure adherence to privacy protocols and best practices.

"Absci's recent breakthrough creating de novo antibodies changed the idea of what's possible for drug discovery," said Jim Gabriele, CEO of M2GEN. "This was just one of the things that excited us about partnering together. Their AI-led approach to targeting biologics to make the drug discovery process more efficient and dramatically impact patients' lives made them an ideal partner. Together, by utilizing our real-word data, we plan to advance personalized cancer treatments in pursuit of a cure."

This partnership maintains Absci's momentum building one of the largest repositories of patient data in the industry to train its generative AI platform for protein drug creation. The company recently partnered with St. John's Cancer Institute to train on their datasets to discover medicines faster.

Bora Pharmaceuticals & Celltrion Partner to Expand OSD Capabilities in APAC Market

Bora Pharmaceuticals Co., Ltd. and Celltrion Asia Pacific Pte., Ltd. recently announced their partnership to contract manufacture and commercialize a range of oral dosage form drugs (OSD) across the APAC region.

The range of oral dosage form products will be manufactured at Bora's Zhunan Site, which is one of the largest US FDA- and MHRA-approved pharmaceutical production facilities in Taiwan. The site has an outstanding compliance record across global regulatory authorities.

The manufactured batches will be used to support Celltrion's regulatory filings for approval in seven countries, and Bora will further support Celltrion to commercialize the products immediately upon approval by utilizing its cutting-edge manufacturing capabilities in complex oral dosage form and superior total-solution services.

Bobby Sheng, CEO and Chairman of Bora, said "We are extremely excited about this new partnership with Celltrion. As a trusted global partner, we look forward to serving our customers with the best technical and quality resources and supporting our partners to expand into various markets around the world."

Bora Pharmaceuticals is a premier international cGMP CDMO specializing in complex oral solid dosage, non-sterile liquids, sterile and non-sterile ophthalmics, nasal sprays, and semi-solids pharmaceutical products for Clinical through Commercial manufacturing and packaging and clinical manufacturing of biologics drug substance. Bora owns and operates seven state-of-the-art CGMP manufacturing facilities (Taiwan and Canada) built to the highest international standards for development manufacturing, packaging, and analytical testing. Our TAA-compliant sites deliver to more than 100 markets around the world. For more information visit www.boracorpcdmo.com

Celltrion is a leading biopharmaceutical company based in Incheon, South Korea that specializes in researching, developing, and manufacturing innovative therapeutics that improve people's lives worldwide. Our solutions include world-class monoclonal antibody biosimilars, such as Remsima, Truxima, and Herzuma, providing broader patient access globally. We have also received US FDA and EMA approval for Vegzelma, and EMA approval for Yuflyma and Remsima SC.

At Celltrion, we pursue sustainable growth by leveraging our experience and assets in the successful biosimilar business to develop new medicines and healthcare platform technologies. We work with a sense of duty to advance patients' wellness and provide them with enhanced access to reliable healthcare. To accomplish this, we adhere to strong internal ethical standards in our daily operations. For more information, visit www.celltrion.com.

Plasticell & LambdaGen Form Collaboration to Develop iPSC-Derived CAR-NK Allogeneic Cancer Immunotherapies

Plasticell Ltd recently announced today it has entered into a strategic collaboration with Singapore-based LambdaGen. Together, the two companies will exploit genome-editing technologies based on synthetic lambda integrases that allow specific insertion of large gene cassettes into the human genome.

The UK-Singapore partnership is in part financed by a EUREKA GlobalStars competitive grant. The funding has been awarded to enable the two organisations to carry out a project – valued at GBP £400,000 (SGD $650,000) – which aims to create a broadly-applicable iPSC-derived allogenic immunotherapy platform.

LambdaGen will produce iPSC lines engineered with chimeric antigen receptors (CARs) and other effectors that enhance the anti-tumour activity of immune cells. Plasticell will use its combinatorial screening technology, CombiCult, to develop optimal protocols to convert these iPSCs into natural killer (NK) cells for allogeneic cancer immunotherapy.

"Cellular immunotherapy using CAR-T cells has revolutionized cancer treatment but these personalized medicines have significant manufacturing constraints and are prohibitively costly. There is a need for alternative "off-the-shelf" immunotherapy products, which can be met by engineered NK cells capable of functioning in an allogeneic setting," commented Dr. Marina Tarunina, Research Director of Plasticell. Our team has longstanding experience in deriving novel, GMP-compliant protocols for robust and efficient differentiation of iPSCs into a variety of haematopoietic lineages including immune cell subtypes suitable for immunotherapy."

"iPSCs can be engineered with various functionalities to increase safety and efficacy of differentiated immune cell products, and to reduce the manufacturing complexity and cost. LambdaGen's technology allows facile insertion of multi-gene cassettes at pre-determined safe harbor sites of the human genome," added Dr. Harshyaa Makhija, CEO of LambdaGen. "We intend to engineer immune cells with multiple genes that increase tumour specificity, persistence, homing, and resistance to the tumour microenvironment, with a view to creating next-generation therapeutic products.

The cellular immunotherapy sector is currently dominated by CAR-T therapies – with over 2100 products in development. NK cells are the second most utilised cell type with over 500 products in development. Genetic modifications (besides CAR-T) which are engineered into cell immunotherapies represent a new approach to enhancing safety and potency. Currently, "armored" cell therapies comprise approximately 10% of assets in development.

Plasticell is a UK biotechnology company developing therapies through precise manipulation of stem cells and more differentiated cell types using award-winning combinatorial screening technology. Plasticell is advancing a number of therapeutic programs, including the expansion of hematopoietic stem cells from bone marrow and cord blood, the manufacture of red blood cells, platelets and immune cells from induced pluripotent stem cells (iPSCs). Plasticell's combinatorial screening technology, CombiCult, allows testing of cell culture variables to derive optimal manufacturing protocols for any given outcome in cell biology, including cell expansion and differentiation, gene transduction and protein production, as well as the provision of human cells for drug screening. Plasticell collaborates with leading universities and industry partners to facilitate discovery and improve product manufacturing in a variety of high value areas such as cell therapy, gene therapy, cancer immunotherapy and drug discovery.

Artelo Biosciences Initiates Phase 2a Portion of its CAReS Trial Evaluating ART27.13 for the Treatment of Cancer-Related Anorexia & Weight Loss

Artelo Biosciences, Inc. recently announced it has initiated the Phase 2a portion of its Cancer Appetite Recovery Study (CAReS), evaluating ART27.13 for the treatment of cancer-related anorexia and weight loss.

"To date, ART27.13 has shown favorable tolerability in patients with anorexia and weight loss related to cancer with no significant negative effects attributed to the experimental drug," said Steven D. Reich, MD, Chief Medical Officer of Artelo. "Based on the positive safety profile and the response pattern observed in the Phase 1b portion of the trial, a dose of 650 micrograms will be administered to patients in the Phase 2a."

The Phase 2a portion of the CAReS study is a double-blind, placebo-controlled design enrolling 40 patients randomly allocated in a 3:1 ratio to receive ART27.12 or placebo once daily for up to 12 weeks. The study is planned to be conducted at approximately 18 clinical sites in five countries.

"We believe ART27.13 can provide a novel way to manage the debilitating effects of anorexia and weight loss in cancer patients who have few, if any, alternatives," said Gregory D. Gorgas, Artelo's President and Chief Executive Officer. "By tripling the number of treatment centers and broadening patient eligibility criteria to include concurrent anti-cancer therapies, our goal is to complete Phase 2a patient enrollment by mid-2024."

ART27.13 is a highly potent, peripherally restricted synthetic, dual G-Protein-Coupled Receptor agonist believed to target the cannabinoid receptors CB1 and CB2, which has the potential to increase appetite and food intake. Originally developed by AstraZeneca plc, ART27.13 has been evaluated in five Phase 1 clinical studies including over 200 subjects where it has demonstrated a statistically significant and dose-dependent increase in body weight in healthy subjects. Importantly, the changes in body weight were not associated with fluid retention and the distribution of the drug enables systemic metabolic effects while minimizing central nervous system-mediated toxicity. Artelo is advancing ART27.13 as a supportive care therapy for cancer patients suffering from anorexia and weight loss, where the current annual global market is estimated to be valued in excess of $2 billion.

The Cancer Appetite Recovery Study (CAReS) is a Phase 1b/2a randomized, placebo-controlled trial of the Company's lead clinical program, ART27.13, in patients with cancer anorexia and weight loss. Anorexia, or the lack or loss of appetite, may result from the cancer and/or its treatment with radiation or chemotherapy. It is common for patients with cancer to lose weight. Anorexia and the resulting weight loss can affect a patient's health, often weakening their immune system and causing discomfort and dehydration. A weight loss of more than 5% can predict a poor outcome for cancer patients and a lower response to chemotherapy. The Phase 1b portion of the CAReS study is designed to determine the most effective and safest dose of ART27.13 for dosing in the Phase 2a stage. The Phase 2a portion of the CAReS study is designed to determine estimates of activity of ART27.13 in terms of lean body mass, weight gain, and improvement of anorexia.

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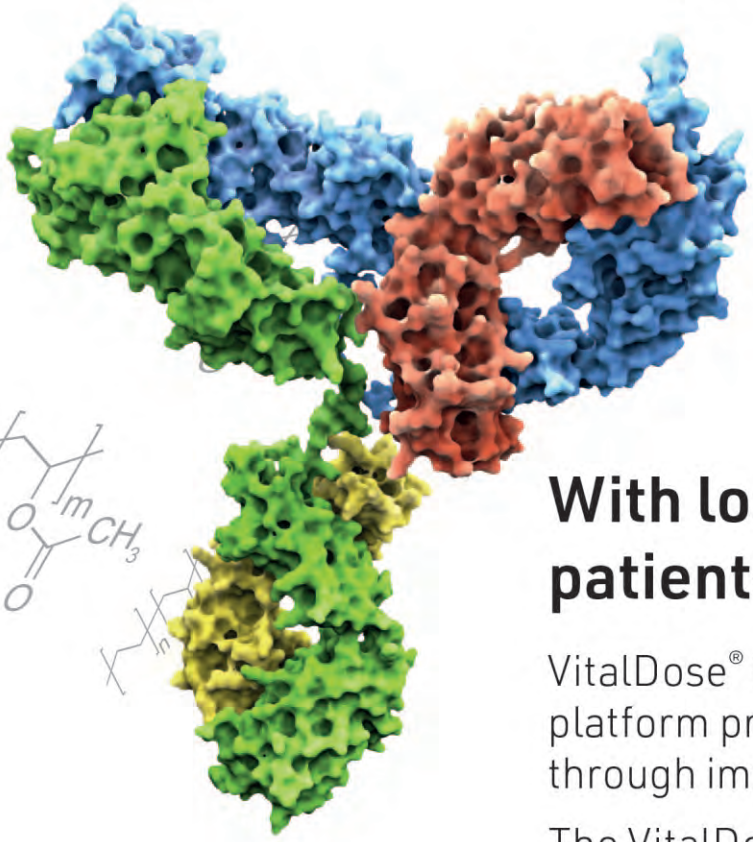
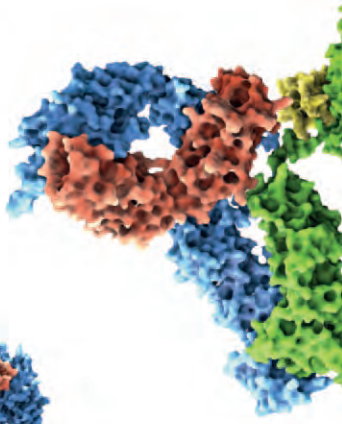
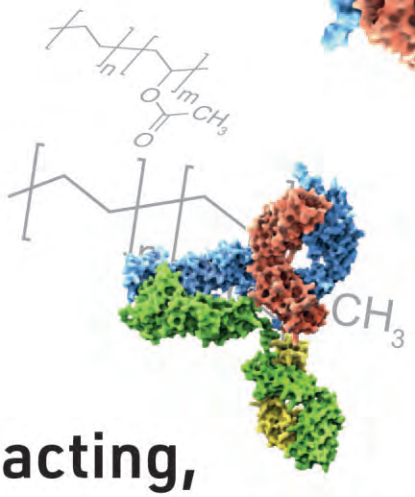






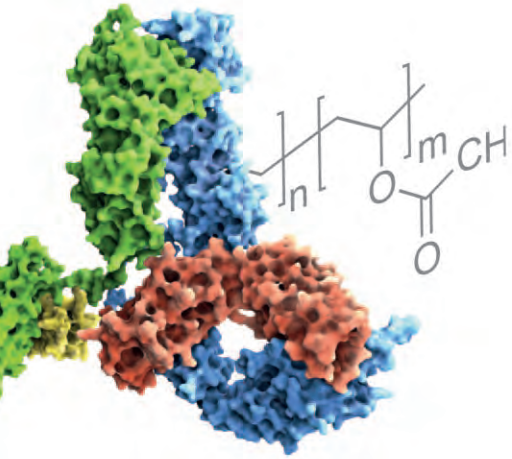
With long-acting, patient-centric therapeutics

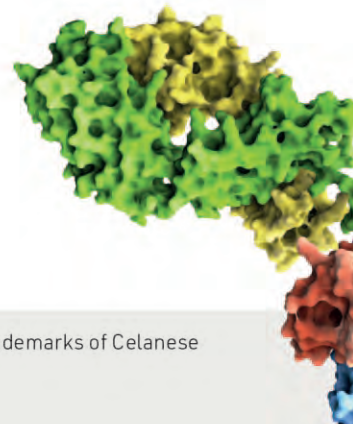
VitalDose® EVA is a copolymer drug-delivery platform providing controlled release through implant and insert dosage forms.

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
- RNA
- Small molecules





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Blue Water Vaccines Announces Corporate Name Change to Blue Water Biotech in Connection With Transition Into Commercial-Stage Biotechnology Company

Blue Water Vaccines Inc. recently announced it has changed its corporate name to Blue Water Biotech, Inc. The corporate name change follows the company's recent acquisition of ENTADFI, an FDA-approved treatment for benign prostatic hyperplasia (BPH), which has commenced Blue Water's transition into a commercial-stage biotechnology company.

"Our recent purchase of ENTADFI is transforming Blue Water into a commercial-stage biotechnology company and this name change is an exciting reflection of that progress," said Joseph Hernandez, Chairman and Chief Executive Officer of Blue Water. "With ENTADFI, we are building a nimble and effective commercial operation that can be leveraged for our current pipeline or future acquired assets. Over the last few months, we have carefully developed a strong and experienced management team to lead us as we navigate this transition, and we are confident that the future of Blue Water and this product are very bright."

Blue Water's commercial team is highlighted by Senior Vice President of Marketing and Business Development, Frank Jaeger, a seasoned marketing and business development executive with extensive experience in the men's health sector. Mr. Jaeger's background and knowledge, along with Blue Water's accomplished management team, will lead the official launch of ENTADFI to generate revenue and impact within the BPH space.

In addition to ENTADFI for the treatment of BPH, Blue Water is developing multiple vaccines to prevent infectious diseases with high unmet need. BWV-201, Blue Water's lead vaccine candidate, is a live attenuated, intranasally delivered, serotype independent Streptococcus pneumoniae vaccine targeting acute otitis media and pneumococcal pneumonia. Additionally, Blue Water is developing a universal influenza vaccine and multiple vaccines using its virus-like particle technology, including Marburg virus disease. Finally, Blue Water is developing a live attenuated, orally delivered Chlamydia vaccine developed with The University of Texas Health Science Center at San Antonio.

Blue Water's common stock will continue to trade under the ticker symbol NASDAQ: BWV.

ENTADFI is an oral, once daily treatment for benign prostatic hyperplasia (BPH) that combines finasteride, a 5α-reductase inhibitor, and tadalafil, a phosphodiesterase 5 (PDE5) inhibitor, offering a more effective treatment option compared to other available therapies. Clinical trials have shown that ENTADFI is more effective in treating BPH symptoms, including urinary frequency, urgency, weak stream, and difficulty initiating or maintaining urination, compared to finasteride monotherapy. Additionally, ENTADFI has demonstrated a favorable safety profile, with fewer adverse sexual side effects compared to finasteride. ENTADFI reduces potential for adverse sexual side effects, making it a preferred choice for men seeking relief from BPH symptoms without compromising their sexual health. ENTADFI has received FDA approval for the indication of initiating treatment of the signs and symptoms of BPH in men with an enlarged prostate for up to 26 weeks.

Aevitas Therapeutics Announces Asset Purchase Agreement With 4D Molecular Therapeutics

Aevitas Therapeutics, Inc. and 4D Molecular Therapeutics recently announced the execution of an asset purchase agreement for 4DMT to acquire Aevitas' proprietary rights to its short-form human complement factor H (sCFH) asset for the treatment of complement-mediated diseases. Under the terms of the agreement, 4DMT will make cash payments to Aevitas totaling up to ~$140 million in potential late-stage development, regulatory, and sales milestones. A range of single-digit royalties on net sales are also payable. The aforementioned payments are payable solely to Aevitas, and 4DMT will be responsible for license payment obligations to University of Pennsylvania, where the sCFH technology was co-invented and co-developed by Dr. Wenchao Song, a Professor of Pharmacology at the Perelman School of Medicine.

Lindsay A. Rosenwald, MD, Fortress' Chairman, President and Chief Executive Officer and Aevitas' Executive Chairman, said "This agreement with 4DMT allows Fortress to focus on acquiring and developing clinical-stage treatments, while potentially expediting the development and commercialization of this preclinical sCFH technology. Partnering with 4DMT further validates the Fortress business model of identifying and developing promising treatments for patients, while pursuing opportunities that potentially maximize shareholder value. We look forward to 4DMT using their vector platform to continue the development of the sCFH asset to potentially treat Geographic Atrophy (GA) and other diseases."

Aevitas' transgene encoding sCFH, a shortened and optimized form of a natural inhibitor of the inflammatory complement pathway, will be combined with 4DMT's proprietary retinotropic R100 vector to form product candidate 4D-175 for treatment of GA secondary to age-related macular degeneration (AMD).

sCFH is an engineered and optimized version of Complement Factor H (CFH) that can fit into AAV vectors with robust expression and functionality confirmed in cultured human cells in vitro, and in multiple preclinical animal models in vivo. Restoring CFH function using the sCFH protein has the potential to restore normal complement regulation and reduce retinal injury that manifests as progressive GA.

"We are pleased to execute this asset purchase agreement with Aevitas to combine an innovative and differentiated preclinical GA product candidate into our large market ophthalmology portfolio which leverages our clinically validated R100 retinotropic vector," said David Kirn, MD, Co-founder and Chief Executive Officer of 4DMT. "This represents continued value generation from our robust product design and development engine to take advantage of the vector modularity of our platform in the ophthalmology therapeutic area."

4DMT is a clinical-stage biotherapeutics company harnessing the power of directed evolution for genetic medicines targeting large market diseases. 4DMT seeks to unlock the full potential of genetic medicines using its proprietary invention platform, Therapeutic Vector Evolution, which combines the power of the Nobel Prize-winning technology, directed evolution, with approximately one billion synthetic AAV capsid-derived sequences to invent customized and evolved vectors for use in our product candidates.

Longeveron Announces First Patient Dosed in Phase 2 Clinical Trial for Aging-Related Frailty in Japan

Longeveron Inc. recently announced the first patient has been treated with Lomecel-B in its Phase 2 clinical trial in patients with Aging-Related Frailty in Japan. The trial aims to enroll 45 patients and its primary objective is to evaluate safety.

"We are excited to announce the dosing of the first patient in our Japanese Aging-Related Frailty trial," said Wa'el Hashad, Longeveron's Chief Executive Officer. "In 2022, Longeveron aligned with the Japan Pharmaceuticals and Medical Devices Agency (PMDA), on the Phase 2 trial design and we hope the data from this trial will provide support for a limited approval under Japan's Act on the Safety of Regenerative Medicine (ASRM), which allows regenerative medicine products to be administered to patients by approved hospitals or clinics under the practice of medicine. This is the first use of our U.S.-manufactured product in Japan, and we look forward to advancing Lomecel-B as a treatment for Aging-Related Frailty in Japan."

Hidenori Arai, MD, PhD, President of the National Center for Geriatrics and Gerontology, and principal investigator of the Phase 2 trial, added "I am pleased to see this clinical trial program advancing, especially given the large unmet need in Japan, where nearly 30% of the population is over the age of 65. I was encouraged by Longeveron's previously announced Phase 2b Aging-Related Frailty study in the US, where subjects receiving a single infusion of Lomecel-B showed a statistically significant and clinically meaningful improvement in walking distance at 9 months post-infusion compared to placebo. I look forward to building on that data in the Japanese population."

The Phase 2 clinical trial is a 3-arm, parallel design, randomized (1:1:1), placebo-controlled, double-blind single infusion study of two different dose levels of Lomecel-B. The trial is expected to enroll 45 patients and has a primary objective of evaluating safety of Lomecel-B as a treatment for Aging-Related Frailty. The trial is being conducted in partnership with the National Center for Geriatrics & Gerontology (NCGG;Nagoya) and Juntendo University Hospital (Tokyo).

Japan is considered to be a "super-aged" society with some 36.4 million individuals aged 65 or older in 2021, representing 29.1% of the population. The overall prevalence of aging-related frailty amongst this demographic is estimated to be 7.9%.

Aging-Related Frailty is an age-associated decline in reserve and function across multiple physiologic systems leading to the inability to cope with stressors. It is characterized by mobility impairment, weakness, fatigue, weight loss, slowness, and low activity and puts individuals at higher risk for poor clinical outcomes, such as infections, falls, fractures, hospitalization, or death.

Longeveron is a clinical-stage biotechnology company developing regenerative medicines to address unmet medical needs. The company's lead investigational product is Lomecel-B, an allogeneic medicinal signaling cell (MSC) therapy product isolated from the bone marrow of young, healthy adult donors. Lomecel-B has multiple potential mechanisms of action encompassing pro-vascular, pro-regenerative, anti-inflammatory, and tissue repair and healing effects with broad potential applications across a spectrum of disease areas. Longeveron is currently advancing Lomecel-B through clinical trials in three indications: hypoplastic left heart syndrome (HLHS), Alzheimer's Disease, and Aging-Related Frailty.

Quotient Sciences Supports Crinetics Pharmaceuticals With Fully Integrated Pediatric Development & Clinical Testing Program

Crinetics Pharmaceuticals and Quotient Sciences have recently announced a partnership to support Crinetics' CRN04894 pediatric program. The partnership will utilize Quotient Sciences' unique Translational Pharmaceutics platform to provide integrated formulation development, clinical manufacturing, and taste assessment studies to accelerate Crinetics' development timeline.

Crinetics is currently developing CRN04894 as an investigational, oral, non-peptide product candidate designed to antagonize the adrenocorticotropic hormone (ACTH) receptor, intended for the treatment of diseases caused by excess ACTH, including Cushing's disease and congenital adrenal hyperplasia (CAH). The pediatric formulation is an oral solution in development for children under two years of age that requires flavoring and sweetening to improve palatability.

Quotient Sciences has over 30 years of experience in pediatric formulation development and taste assessment studies. To support Crinetics' CRN04894 pediatric program, Quotient Sciences will carry out an integrated, real-time adaptive GMP clinical manufacturing campaign alongside a Phase I clinical study in healthy volunteer subjects to assess the taste and palatability of several oral solution formulations. The development program will evaluate different flavoring agents and sweetener levels in order to identify the optimal formulation.

"There is an art to the development of taste-masked oral products for pediatric indications," said R. Scott Struthers, PhD, Founder and CEO of Crinetics Pharmaceuticals. "Quotient Sciences' expertise in improving the taste, smell, and texture of oral formulations makes them the ideal partner for Crinetics' pediatric clinical programs."

Mark Egerton, PhD, CEO of Quotient Sciences, added "We are delighted to partner with Crinetics to support the development and clinical testing for CRN04894. With the industry focused on developing acceptable and palatable pediatric formulations to address patient need and regulatory requirements, we are fortunate that our integrated Translational Pharmaceutics platform offers customers the opportunity to accelerate their development timelines, so that patients can access much-needed medicines faster."

Quotient Sciences is a drug development and manufacturing accelerator providing integrated programs and tailored services across the entire development pathway. Cutting through silos across a range of drug development capabilities, we save precious time and money in getting drugs to patients. Everything we do for our customers is driven by an unswerving belief that ideas need to become solutions, and molecules need to become cures, fast. Because humanity needs solutions, fast. For more information, visit quotientsciences.com.

FORMULATION FORUM

LIPIDSOL®: Liposomes - Chemistry, Properties & Applications of Lipid Nanoparticles

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

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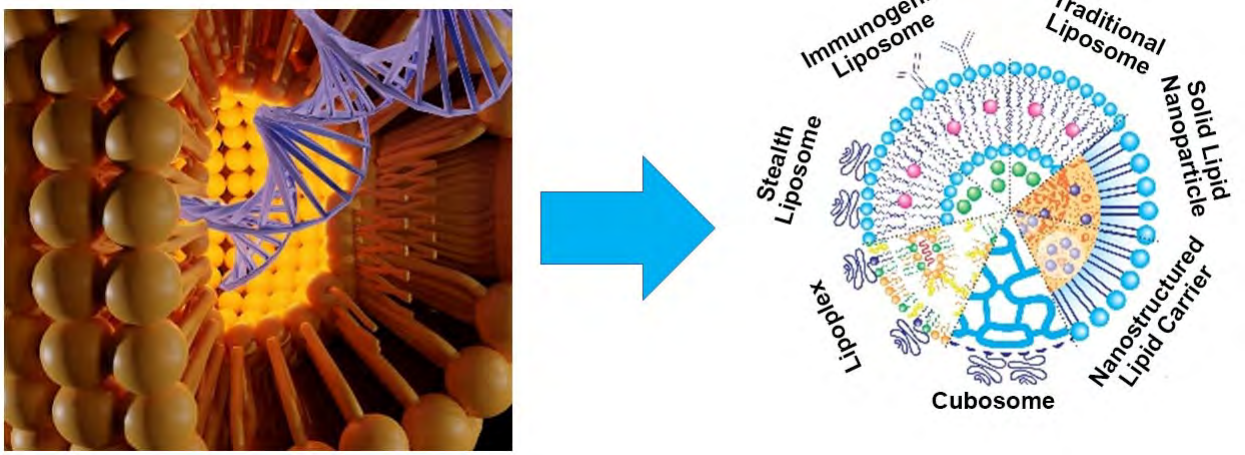
INTRODUCTION

LipidSol®, Ascendia's lipid nanoparticle (LNP) platform technology, is aimed to improve the delivery of therapeutic modalities entrapped in lipid structures varying with different compositions of long chain fatty acids and polar headgroups. Designed specifically to increase maximum entrapment in the LNP interior, LipidSol, can adopt different shapes and sizes and can be recognized by different assemblies as shown in Figure 1.

The landscape of LNPs is continuously evolving as more and more challenging therapeutic modalities are discovered in the preclinical phase that require parenteral route of administration with controlled drug delivery.[1] In a recent survey by the chemical abstract services (CAS) between 2000 and 2020, focusing on newer trends after the era of traditional liposomes, more than 1700 documents related to LNPs were published as patents and non-patented articles in journals and books (Figure 2).[2] In LNP subcategories, immunogenic and cationic liposomes are the fastest growing areas followed by stealth liposomes, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and cubosomes.

As indicated, these LNPs play an important role in the formulation and delivery of a number of modalities. Liposomes were discovered in 1965; since then, they have been used as carriers in the transport of hydrophobic and/or hydrophilic, small and large therapeutic modalities, including proteins, peptides, and nucleic acids. A number of drugs using liposome technologies have been commercialized successfully for treatment of cancers, inflammation, and other rare diseases.[3] Other structural modifications of LNPs include SLNs, NLCs, immunogenic liposomes engineered with conjugated antibodies (immunogenic) for targeting diseases tissues, and lipoplexes engineered with cationic lipids for encapsulation of vaccines and biologics. Like other LNPs, the

FIGURE 1



LipidSol® – Assemblies of Lipid Nanoparticle Structures

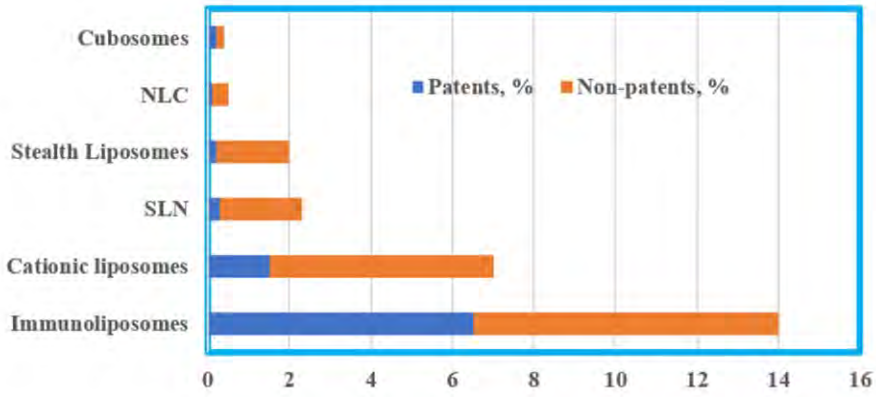
cubosomes designed with low melting lipids and polymers are also recognized for their longer circulation and effective delivery of drug molecules.[4]

CHEMICAL STRUCTURE OF LIPIDS

Before getting into the details of liposomes, let's first examine the structure of these lipids, preferably the di-acyl phosphatidylcholines, wherein, the di-acyl chains at the glycerol backbone represent the lipophilicity of the lipids and the phosphatidylcholine moiety represents the polar headgroup.[5] The glycerol backbone is tethered with fatty acid chains at the *sn*-1 and *sn*-2 positions, and the headgroup composed of phosphate and choline moieties are attached at the *sn*-3 position of the natural lipids. These groups are susceptible to membrane phospholipases; for example, the fatty acid chains at *sn*-1 and *sn*-2 are susceptible to phospholipase A_1 and A_2, respectively; whereas the phosphate and choline moieties are prone to hydrolysis by phospholipase C and D, respectively.[6]

In spite of the susceptibility to enzymatic degradations, these phospholipids are important carriers for delivery of payload through systemic circulation.[7] The structural

FIGURE 2



Number of LNP-related documents (patents and non-patents) from CAS database during 2000-2020.

TABLE 1

Name/Route	API	Liposome Composition	Indication	Year Approved
Abelcet®/IV	Amphotericin B	DMPC:DMPG	Acute fungal infections	1995
Ambisome®/IV	Amphotericin B	HSPC:DSPG:Chol	Fungal infections	1997
Amphotec®	Amphotericin B	Cholesteryl sulfate	Fungal infections	1996
Caelyx®/IV	Doxorubicin	DSPE-PEG2000: HSPC:Chol (5:56:39)	Ovarian and breast cancer, Kaposi's sarcoma	1996
DaunoXome®/IV	Daunorubicin	DSPC:Chol (2:1)	AIDS-related Kaposi's sarcoma	1996
Depocyt®/Spinal	Cytarabine/Ara-C	DOPC, DPPG, Chol, triolein	Neoplastic meningitis	1999
DepoDur®/Epidural	Morphine sulfate	DOPC, DPPG, Chol, triolein	Pain management	2004
Doxil®/IV	Doxorubicin	HSPC:Chol:DSPE-PEG2000	Ovarian and breast cancer, Kaposi's sarcoma	1995
Epaxal®/IM	Hep V virus/RGSB	DOPC:DOPE (75:25)	Hepatitis A	1993
Exparel®/IV	Bupivacaine	DEPC:DPPG: Chol: Tricaprylin	Pain management	2011
Fungizone®/IV	Amphotericin B	DMPC:DMPG	Systemic fungal infections	1997
Inflexal® V/IM	Hemogglutinin of influenza virus strains A and B	DOPC:DOPE (75:25)	Influenza	1997
Lipodox®	Doxorubicin	DSPC, Chol, DSPE-PEG2000	Breast cancer	2012
Lipusu®/IV	Paclitaxel	Non-PEG ylated	NSCLC, esophageal cancer	2020
Marqibo®/IV	Vincristine	SM:Chol (60:40)	Acute lymphoblastic leukemia	2012
Mepact®/IV	Mifamutide	DOPS:POPC (3:7)	Osteosarcoma	2004
Myocet®/IV	Doxorubicin	EPC:Chol (55:45)	Metastatic breast cancer	2000
Octocogalfa® (advate)/IV	Factor VIII	PEG lipid	Hemophilia A	2009
Onivyda®/IV	Irinotecan	DSPC:MPEG2000:DSPC (3:2:0.015)	Pancreatic cancer	2015
ThermoDox®/IV	Doxorubicin	DPPC, MSPC, DSPE-PEG2000	Hepatocellular carcinoma	2014
Visudyne®/IV	Verteporfin	DMPG, EPG	Choroidal neovascularization	2000
Vyxeos®/IV	Daunorubicin/Cytarabine (1:5)	DSPC:DSPG:Chol (7:2:1)	Acute myeloid leukemia	2017

Abbreviations: Ingredient: Chol - cholesterol; PC - phosphatidylcholine; PG - phosphatidylglycerol; PE - phosphatidylethanolamine; PS - phosphatidylserine; DEPC - Dierucoyl PC; DMPC - dimyristoyl PC; DMPG - dimyristoyl PG; DOPC - dioleoyl PC; DOPE - dioleoyl PE; DOPS - dioleoyl PS; DPPG - dipalmitoyl PG; DSPC - distearoyl PC; DSPE - distearoyl PE; DSPG - distearoyl PG; EPC - egg PC; HSPC - hydrogenated soy PC; MSPC - monostearoyl PC; PEG - polyethylene glycol; POPC - palmitoyloleoyl PC; SM - sphingomyelin
Route: IM - intramuscular; IV - intravenous

Summary of Liposome-Based Approved Drugs[2,3,22]

modifications of these lipids make them less susceptible for enzymatic degradation. For example, the acyl chains modified with an ether linkage can lead to longer circulation and act as an oncology drug, and may lead to greater therapeutic efficacy in encapsulated liposomes.[8] An ether lipid, for example, with a O-C18 fatty acid at the sn-1 position, and an O-methyl group at the sn-2 position, is highly stable, which makes it a good candidate as "edelfosine" for treatment of certain cancers.[9]

LIPOSOMES AS A CARRIER FOR DRUG DELIVERY

Since its discovery in mid 1960s, liposomes have been used extensively in the formulation of many drug molecules.[10] A handful of liposome-based drugs have been marketed commercially (Table 1).[2] Because of their unique structures with inner aqueous cavity and a lipophilic bilayer interior, the drug molecules, amphiphilic and/or hydrophobic in nature, get preferentially partitioned into these assemblies. Thus, these lipid assemblies can act as carriers in transporting the molecules to target tissues.[11] These lipid molecules used as LNPs can be designed with a wide spectrum of structures typically derived from long saturated or unsaturated fatty acid chains as the lipophilic interior and polar headgroup as the hydrophilic moieties facing the exterior aqueous phase. There have been continued interest in designing smarter molecules with a headgroup to provide and electrostatic charge to prevent flocculation or aggregation and to enable longer circulation in the blood.[12] These modifications include replacing the PC headgroup with phosphatidyl ethanolamine (PE), phosphatidyl glycerol (PG), phosphatidyl serine (PS), and/or phosphatidyl inositol (PI).[13] Applications of liposomes composed of phospholipids, however, could be limited by its shelf-life and its ability to protect encapsulated drugs due to high permeability leading to leakage of its payload through bilayer membranes. Thus, cholesterol or sterol is used to overcome membrane flexibility, permeability, and stability.[14] Liposomes with other ingredients, such as vitamin E or Vitamin E-TPGS, PEGs incorporated in bilayers, serve as carriers in transporting and protecting the molecules from environmental pHs, enzymatic, and chemical changes as well as shielding them from temperature and ion fluctuations, thus improving the stability, shelf-life and bio-distribution.[15]

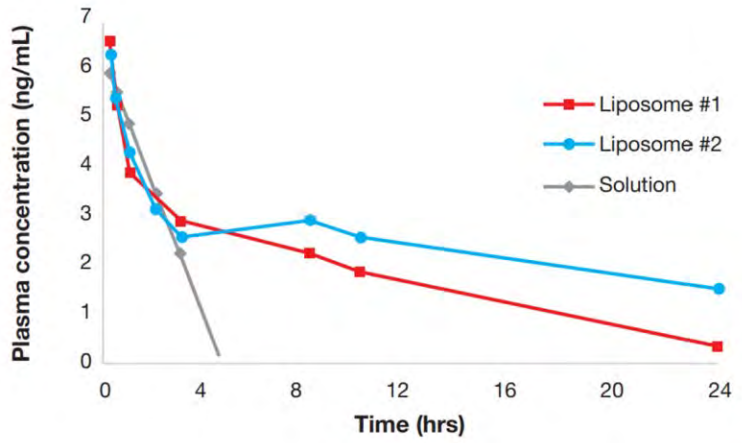
Phospholipids with varied chain lengths and fatty acid compositions and headgroups, like PC, PE, PG, and PS, among others, are spontaneously aggregate in aqueous solution to form lipid particles ranging between 20 nm and 1000 nm. The insoluble molecules can partition into the lipid interior if hydrophobic, or if hydrophilic, can partition in the aqueous interior of liposomes. These liposomes can be prepared via simple agitation to sonication to homogenization methods as small vesicles (SUVs) with particle size of 20-100 nm, large unilamellar vesicles (LUVs) with particle size diameter of 100-1000 nm, or multilamellar vesicles (MLVs) with diameters of >500 n. Liposome particle size is a critical attribute for drug encapsulation and circulation half-life. Smaller size liposomes circulate longer than larger sizes without being engulfed by phagocytes.[16] Several drugs approved in liposomes typically have the particle size range of 100 nm or less.[17] The particle size of liposomes is controlled by extrusion, sonication, and homogenization, and is measured by dynamic light scattering, size exclusion chromatography, nuclear magnetic resonance spectroscopy, and light microscopy.

Lipid headgroup plays an important role in drug delivery at the cellular level.[18] The surface charges created by positive, negative, and/or zwitterionic moieties contribute to potential to cross the membrane bilayers, allow partitioning and migration of drugs from the outer to inner membranes, and the stability of liposomes, in general. For instance, liposomes with higher charges around the membrane and contributed by, for instance, PG or PE, may provide much better stability due to charge repulsions than those with neutral lipid membranes. A zeta potential -30 mV or >30 mV can lead to stronger charge repulsion and particle segregation in these suspensions than those with lower zeta potential.[19]

Many anti-cancer drugs are typically formulated in liposomes or LNPs due in part to most of those drugs are poorly soluble and cytotoxic. Therefore, better and efficient encapsulation methods are required to

Ascendia scientist working with NanoAssemblr® Blaze for manufacturing of lipid nanoparticles.

FIGURE 3



PK profile of drug encapsulated in DMPC/Chol/DSPE (Formulation 1), Egg PC/Chol (Formulation 2), and aqueous solution.

solubilize, protect, and transport these molecules to the target tissues to enhance efficacy and reduce drug toxicity. As evident from Table 1, the earliest approved drug doxorubicin was formulated in liposomes and approved for treatment of ovarian cancer followed by the approval of Epaxel in liposomes to deliver the hepatitis A vaccine earlier in 1993.[20,21]

CASE STUDY

In a case study, liposomes were encapsulated with carvedilol (@7%) and prepared by dissolving the drug and lipids in ethanol. In formulation F1, liposomes were composed of DMPC:Cholesterol:DSPE (52:21:22), whereas, in formulation F2, the liposomes were composed of egg PC:Chol (65:27).23 The ethanolic solution of lipid and drug was heated at 60°C, which was then injected into 0.9% saline. Following high pressure homogenization at 12,000 PSI through 10 cycles, the lipid suspensions were sterilized by filtration through a 0.22-micron PTFE filter. The free drug was removed through dialysis in 0.9% saline, and the lipid suspensions with 75-150 nm particle size were obtained by extrusion with higher encapsulation efficiency (ca. 80%-90%) and unimodal distribution (PDI 0.12-0.19).

For *in vivo* studies, carvedilol was single dosed at 2.5 mg/kg, and pharmacokinetic (PK) data from three animal groups (DMPC liposome formulation #1 in Group 1, Egg PC liposome formulation # 2 in Group 2, and aqueous solution in Group 3) were collected and are shown in Figure 3. *In vivo* data in rats following iv administration shows that drug continues to circulate longer and is maintained in plasma over 24 hours as compared to drug in aqueous solution, which is cleared out in < 4 hours.

SUMMARY

This article described the latest trends in LNPs as more and more novel therapeutic modalities discovered can't be handled by traditional microemulsions or nanoemulsions. Ascendia's LipidSol technology encompasses all the lipid nanoparticles to address a variety of therapeutic modalities that can't be solubilized and delivered to diseased tissues by traditional oral, injectable, or topical routes of administration. In cases like these, LipidSol enables the encapsulation of drugs in LNPs by the utilization of fatty acids and polar headgroup entities that are commercially available and listed in the FDA inactive ingredient database (IID). In addition to traditional liposomes, other LNPs, such as immunogenic and stealth liposomes, SLNs, NLCs, and cubosomes, will play an important role as more challenging modalities are discovered. Ascendia's footprint in innovative platform technologies, for instance LipidSol, will continue to address the challenges in injectable formulations requiring controlled delivery of small molecules, biologics, and genes. ◆

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IMMUNOLOGY

Innovation Gathers Momentum Amid New Scientific & Technological Breakthroughs

By: Patrick Larcier, PhD

INTRODUCTION

The fields of immunology and immuno-oncology have seen some significant advances and changes throughout the past decade or more, all of which are bringing new hope to patients and healthcare systems. In the next 5 years, these advances are expected to gather momentum amid new scientific and technological breakthroughs.

In particular, immunology has witnessed three major trends, each crucial to continued advancement in the field. These are the next generation of immunological treatments, new approaches to research globally, and the arrival and growing importance of biosimilars. As we look forward to 2023 developments, we can expect to see some significant results in the clinic and on the market.

A NEW AGE OF IMMUNOLOGICAL TREATMENT

The age of immunology really began in the late 1990s and early 2000s with Tumor Necrosis Factor (TNF) alpha inhibitors and vascular endothelial growth factor (VEGF) inhibitors. Products such as infliximab (Remicade®) and adalimumab (Humira®) to treat a host of autoimmune disorders and products like bevacizumab (Avastin®) and others to treat cancer marked the arrival of this area of innovation.

The next major developments came more than a decade later with the emergence of a new generation of monoclonal antibodies, such as pembrolizumab (Keytruda®) and nivolumab (Opdivo®), to treat different types of cancer, bringing new approaches to these difficult pathologies. Since then, monoclonal antibodies have become the top selling drugs in the pharmaceutical market.[1]

Even more recent is the approval of several Janus kinase (JAK) inhibitors to treat a variety of chronic inflammatory disorders, such as rheumatoid arthritis, ulcerative colitis, and atopic dermatitis. These treatments tackle inflammatory conditions in a different way to classic treatments, offering hope of both symptom relief and slowing progression of disease.

Nevertheless, there have been some safety concerns raised with some JAK inhibitors, including tofacitinib (Xeljanz®) for the treatment of arthritis and ulcerative colitis, underscoring the importance of safety monitoring in late-stage clinical trials and through registries to assess their impact on a larger pool of patients.

RESEARCH REACHES THE NEXT LEVEL

New approaches to research, both with biologics and small molecule products, have led to therapies for pathologies that previously had no or very limited treatments.

Until recently, atopic dermatitis was managed with topical therapies, but research carried out by biotech and specialist pharma companies has paved the way for more holistic treatment options, including dupilumab (Dupixent®) and tralokinumab (Adbry® or Adtralza®), an injection that gained European Medicines Agency (EMA) approval in early 2021 and US Food and Drug Administration (FDA) approval later the same year.

The first treatment for active systemic lupus erythematosus in decades, anifrolumab (Saphnelo®), brings hope to patients suffering from this debilitating autoimmune disease. While used in combination with immunosuppressants, it marks a huge step forward after monoclonal and polyclonal antibody approaches proved unsuccessful.

Another disease area companies have struggled to successfully treat is Alzheimer's disease. However, the approval of aducanumab (Aduhelm®) followed by the recent approval of lecanemab (Leqembi®) opened the door to addressing the underlying biology of the disease and slowing cognitive decline of some patients with the disease. However, concerns have been raised as to whether the benefits justify the risks, side effects, and cost of the drug.[2]

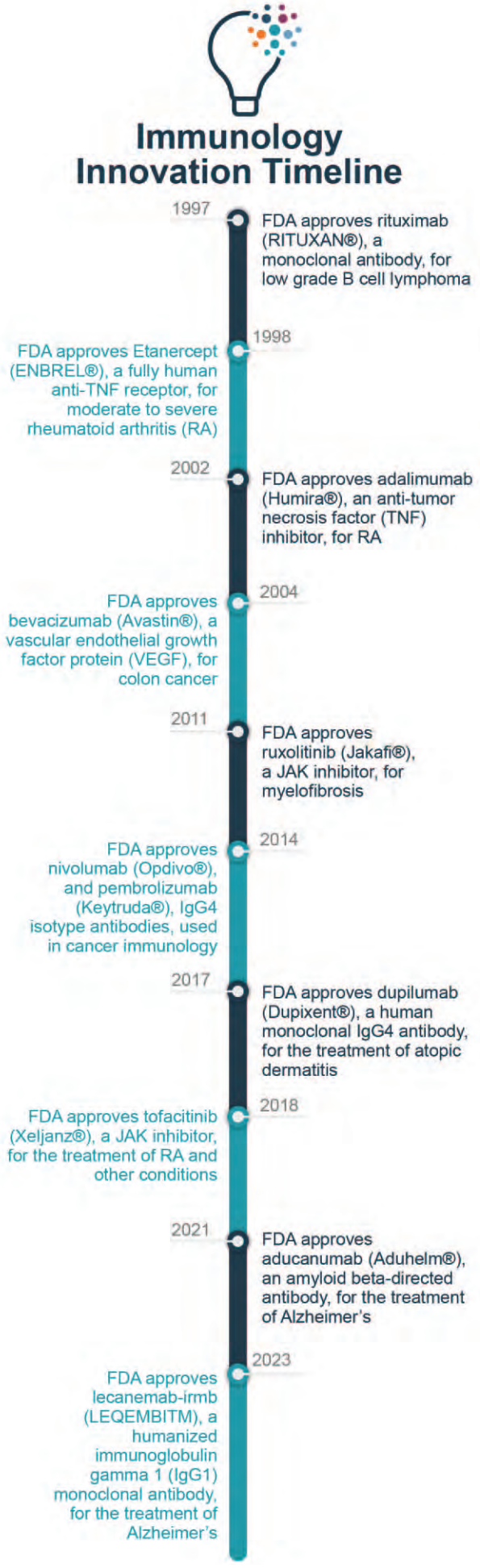
Perhaps one of the most prominent developments since 2020 has been in the area of mRNA research. While the best-known research and early success has been with the COVID-19 vaccines, companies are also targeting other viral diseases, such as the Zika virus and HIV, and several biotech companies have ongoing programs focused on cancer vaccines, with a number in clinical trials. There have been some promising results with an antigen specific T cell response, including prolonged disease-free survival in some clinical trials.[3]

One key consideration with mRNA discoveries is the complexity of scaling up good manufacturing practice (GMP)-grade production, given how new the field is from a development perspective. Equally, it will be important to set up registries or long-term follow-up of patient cohorts to monitor the safety of these products.

Beyond drug research, another area that has seen significant advances in recent years is artificial intelligence, in particular, AI and the Internet of Medical Things. These technologies are important for innovation because they provide insight into the different types of cells in the immunology system - their roles, their importance, how they interact with each other, and pathologies in the field of immune disorders - in a way that is difficult to observe through traditional human research. The observations enabled by these technologies provide new insights into potential approaches to treat or even prevent certain pathologies.

THE ADVENT OF BIOSIMILARS

While many of the innovations of the past decade or more have created new hope for patients, the cost of many of these products has been an issue for healthcare systems. Pharmaceutical companies have fought to protect their patents, but healthcare systems, particularly in Europe, have been keen to support the development of biosimilars. In September 2022, the EMA and the Heads of Medicines Agency (HMA) issued a joint statement noting that biosimilars that have been approved in the EU are interchangeable with the reference medicine or a comparable biosimilar.[4]



The UK's National Health Service, for example, has welcomed biosimilars and the cost savings these create, noting after negotiations in 2018 that using the best-value adalimumab biosimilar product would save the NHS £300 million of its previously £400 million-per-year spending on the product.[5]

While there are development challenges to bringing a biosimilar to market, requiring expertise and investment by the companies involved, these products are broadly welcomed, at least in the EU, and make access to life-saving treatments more affordable for countries and patients. The US has been slower to adopt biosimilars, but they are starting to be seen as more attractive options by healthcare stakeholders.

INTO THE FUTURE WITH INNOVATION

The improvements in research, the arrival of new treatments on the market, and the use of novel technologies all pave the way for more breakthroughs around 2025. In 2021, for example, the FDA approved 50 innovative drugs, offering more treatment options for patients in the US.[6]

Importantly, many of these products are in therapeutic categories in which there is not a huge armamentarium, such as atopic dermatitis, and in areas in which there is enormous unmet need, such as Alzheimer's disease. Research in this therapeutic category is not only being conducted with biotech products such as monoclonal antibodies, but also with small molecules. Animal studies of neuron-targeted treatment based on zinc-finger DNA-binding proteins (ZFPs) were found to lower brain levels of mutant huntingtin (mHTT) protein in a Huntington's disease mouse model and extend survival.[7]

The same is true in the area of multiple sclerosis in which one biotech leader, Biogen, which has an extensive MS portfolio, has been exploring small molecule treatments for the disease in partnership with other innovator companies.[8]

We will also see more biosimilars come to market in the next few years, including from companies that developed the originator product as they seek to preserve their market share. As an example, Kyowa Hakko Kirin received approval in Japan for a biosimilar of its own product darbepoetin alfa for the treatment of anemia associated with chronic renal failure and cancer chemotherapy.[9]

PREPARING FOR 2023 WITH THE REGULATORS

As developers of innovative products look to extend their research into new areas, it is important to ensure early dialogue with the health authorities, especially during the development phase. Discussing and getting validation on the approach can help ensure development plans are in line with regulators' expectations.

Ideally, discussions should start as soon as a company has a potential drug candidate and an idea of where they want to go with the target product profile (TPP). Given the global nature of drug development, it's preferable to have discussions at least with the regulators in the two major regions, the US and the EU, starting with an initial meeting followed by continuous dialogue.

While there is often a belief that regulators are not supportive of drug development, the evidence is to the contrary, with most regulators eager to support innovation and help bring new products to patients in need. Whether through formal or informal discussions, regulators provide a lot of feedback and recommendations to companies that liaise with them.

The FDA, EMA, and the UK's MHRA all have formal avenues that support development. For example, the EMA's PRIME scheme offers enhanced interaction and early dialogue between the regulator and sponsors developing medicines that target an unmet medical need.[10] FDA's INTERACT is an informal meeting early in product development that is offered for programs that are neither too premature nor too advanced in development.[11] In the UK, the Innovative Licensing and Access Pathway (ILAP) seeks to help sponsors bring their products to market faster by providing in-depth regulatory and other stakeholder input.[12]

Increasingly, companies are starting to appreciate the importance of initiating such a dialogue with the regulators and, as the health authorities place greater emphasis on these discussions, these interactions are likely to increase.

Other important avenues for bringing products to the market in the coming years will be to consider pathways such as compassionate use programs that allow companies to propose pre-submission use of their products for patients with serious unmet needs, such as cancer and immune disorders. Several countries in Europe have either named patient programs or in a few countries (Spain, Italy, France, and Sweden) small cohorts of patients who could possibly all be on the same protocol.

These programs not only allow patients to get the help they need sooner, but are also a tool that sponsors can use to gain greater visibility for their products by

physicians, patients, and key opinion leaders, while at the same time gathering more real-world and safety data on the product. Having real-world data will become of greater importance in future as companies not only seek to demonstrate the safety and efficacy of their product, but also demonstrate its usefulness to the health technology assessment bodies for reimbursement.

One regulatory consideration for companies going into 2023 and beyond will be how to address the issue of the pediatric investigation plan (PIP). Depending on prevalence figures of disease in the pediatric population, there are likely to be tighter requirements with regard to demonstrating the product can be used by children under 16, whether the same formulation or one adapted to that population.

While this does present a constraint for companies, regulators are focused on ensuring pediatric patients, particularly those with rare or life-threatening diseases, have access to efficacious and safe treatments.

A PROMISING DEVELOPMENT FUTURE

The year ahead is likely to bring breakthroughs in drug and biologic developments. Managing the development and the regulatory pathway will require a thoughtful, preferably global strategy, focusing on patient need and the expectations of the health authorities. ◆

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BIOGRAPHY

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MICROCRYSTALLINE CELLULOSE **(Core/Content)**	75.76 mg
SODIUM STEARYL FUMARATE **(Core/Content)**	29.29 mg
COLLOIDAL SILICON DIOXIDE **(Core/Content)**	7.58 mg
POLYVINYL ALCOHOL, UNSPECIFIED **(Tablet/Capsule coat)**	11.72 mg
POLYETHYLENE GLYCOL **(Tablet/Capsule coat)**	5.92 mg
TALC **(Tablet/Capsule coat)**	4.33 mg
FERRIC OXIDE YELLOW **(Tablet/Capsule coat)**	0.32 mg
TITANIUM DIOXIDE **(Tablet/Capsule coat)**	7 mg
FD&C RED NO. 40 **(Tablet/Capsule coat)**	
FD&C BLUE NO. 2 **(Tablet/Capsule coat)**	

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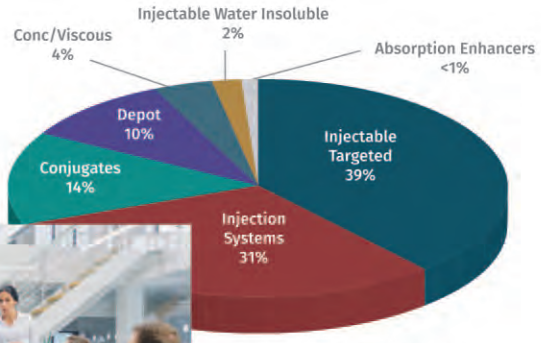

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ION EXCHANGE EXCIPIENTS

Tackling Patient Compliance With Oral Drug Formulations Using Ion Exchange Resins

By: Amie Gehris

INTRODUCTION

Oral administration is the most common way people take their medications. In principle, oral medications are convenient because most are easy to swallow, and patients can self-administer without the help of healthcare staff or trips to the doctors. They come in many forms; solid tablets and capsules, powders, granules, syrups, suspensions, and, more recently, chewable tablets and gummies. All delivery forms offer painless administration with a precise quantity of the active pharmaceutical ingredient (API) that can be easily stored at home.

While the majority of individuals use oral medicines without incident, they are known to have a very bitter taste that can inhibit patient compliance. Tablets and capsules are designed to be swallowed whole and, therefore, are not in contact with the taste receptors for long enough to cause a reaction to the bitter taste of many drugs. But liquids, soluble, and chewable formulations are often in the mouth much longer than solid formulations, so the API's bitter taste can cause problems with patient compliance.

In certain patient groups, namely geriatric and pediatric, problems can also arise with solid oral formulations as they can often have difficulty swallowing the tablets or capsules.[1] 60% of individuals in one study reported they found it difficult to swallow tablets or capsules, and 69% admitted to not taking a medication because it was difficult to swallow.[2] To combat this, many medications for these individuals come in easy-to-administer forms such as liquids or soluble tablets. However, this then causes issues with taste, with an excess of 90% of pediatricians reporting that a drug's taste and palatability are the most significant barriers to patients completing the treatment.[3] For geriatric and pediatric patients, the bitter taste and the ability to easily take medications are significant factors in patient compliance.

THE USE OF ION EXCHANGE RESINS

Ion exchange resins (IERs) have been used for many years to aid in pharmaceutical formulations, and one of the main attributes is flexibility for the development of controlled-release formulations, such as suspensions, tablets, capsules, and orally disintegrating tablets (ODTs). These polymers are capable of exchanging ions within a solution that is passed through them. IERs enable taste-masking of bitter drugs, stability of unstable materials, and solubility enhancement of poorly soluble drugs.

In pharmaceutical applications, this functionality can be used to create more powerful, functional excipients with a direct impact on the availability of a drug and patient compliance. Drugs can be loaded onto the resins by an exchanging reaction, forming a drug-resin complex (resinate). The drug is released from the resinate by exchanging with ions in the gastrointestinal fluid, rather than in the mouth, followed by drug diffusion. Because the API is not released in the mouth, no bitter taste is registered. As they are high molecular weight water-insoluble polymers, the resins are not absorbed by the body and are therefore inert.

APIs require different drug delivery systems, from edibles such as gummies to taste-masked, controlled-release suspensions. IERs enable effective drug formulation in a broad range of uses from tablet disintegration and solubility enhancement to controlled API release and improved taste.

The versatility of IERs enables them to be exploited more

widely as drug delivery vehicles for oral formulations like tablets, capsules, and syrups. In addition, by selecting specific ion exchange chemistry and platforms, it is possible to develop better patient experiences and outcomes.

MASKING THE BITTER TASTE

Humans have evolved to use taste as one of the first tests to determine if a substance is edible as opposed to potentially toxic. Therefore, it's no surprise patients dislike and avoid taking medication when it tastes unpleasant.

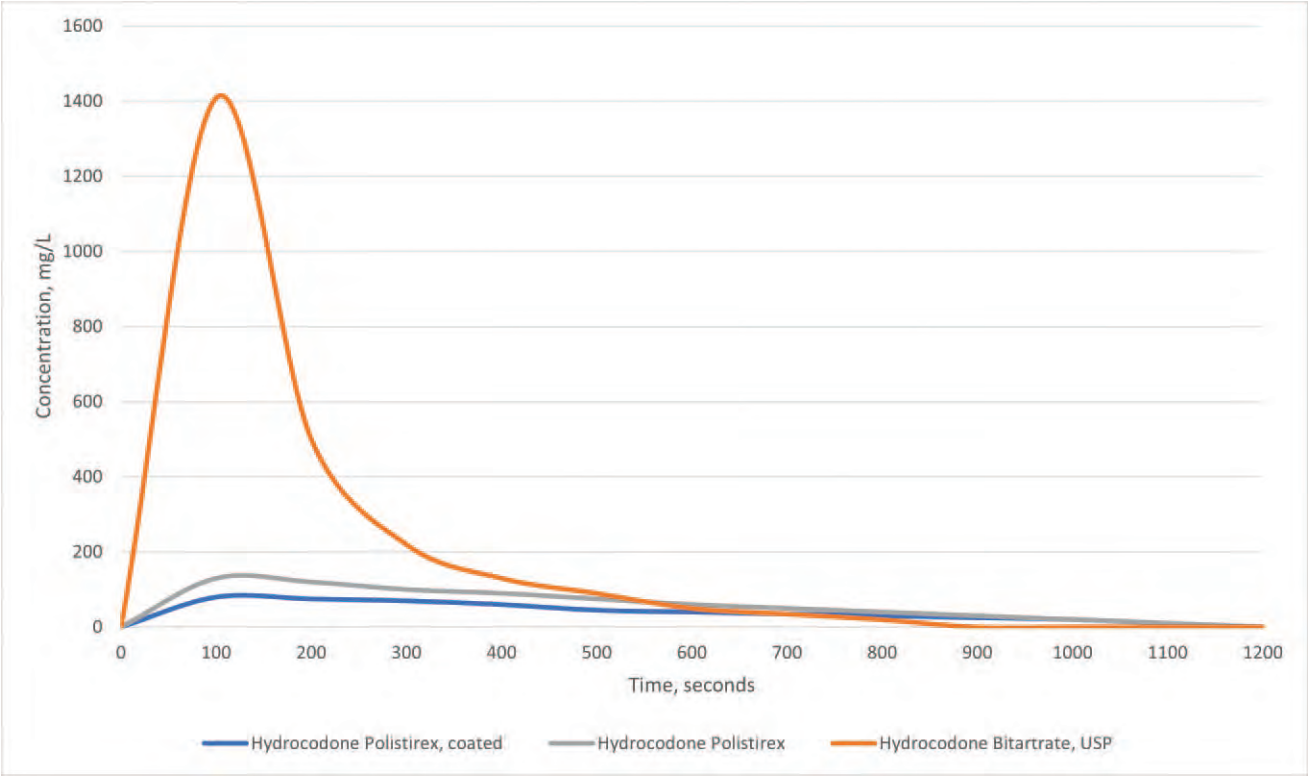
There are many ways to mask the bitter taste – adding flavors or sweeteners, encapsulating or coating the API, altering the pH of the API, or using IERs. The most appropriate method is dependent upon the specific API, degree of bitterness, intended final form, and the manufacturing process. The inherent bitterness of some APIs cannot be masked by adding flavors or sweeteners alone. In addition, adding sweeteners may be undesirable for patients with diabetes, fructose intolerance, or aspartame intolerance (ie, phenylketonurics). Poorly adsorbed flavor additives and non-digestible sweeteners can also produce laxative effects.

Limiting dissolution of the API in a patient's mouth is an alternative that can be achieved via API complexation using IERs. This method binds the API so the release in salivary pH is insufficient to produce a bitter taste, thus improving compliance. Additionally, buccal dissolution allows the selection of taste-masking formulations, helping manufacturers to optimize their taste-masking methods in vitro and show differences between formulations.

A study was conducted to demonstrate the use of IERs to mask the taste of hydrocodone, a cough and cold drug. DuPont™ AmberLite™ was used to test drug loading. These resins range from weak to strong acids and have different ionic forms – hydrogen, potassium, and sodium. Buccal dissolution was measured after loading APIs onto polistirex (AmberLite IRP69) and the effect of coating on buccal release was assessed using 10% ETHOCEL™.

The taste of hydrocodone was successfully masked by synthesizing the API with polistirex resin or coating the resinate with 10% ETHOCEL. Both formulations released significantly less API when exposed to simulated saliva than the control (Figure 1). The coated formulation achieved greater taste-masking with an efficiency of 94.3% compared to 91.7% of the polistirex alone, thus demonstrating the complementary nature of ion exchange and cellulosic coating technologies.

FIGURE 1



Buccal dissolution of hydrocodone in simulated saliva, pH 6.2, synthesized with a 3:1 resin:drug weight ratio.

AIDING TABLET DISINTEGRATION & SOLUBILITY

ODTs have gained much attention as a preferred alternative to conventional oral dosage forms such as tablets and capsules. They are designed to disintegrate rapidly in the mouth upon contact with saliva and allow oral drug delivery with little chewing or the need for water. ODTs release the API in the mouth for absorption through local oromucosal tissues and through pregastric (eg, oral cavity, pharynx, and esophagus), gastric (ie, stomach), and postgastric (eg, small and large intestines) segments of the gastrointestinal tract. The administration of ODTs circumvents problems such as difficulty in swallowing traditional solid oral dosage forms. Therefore, they offer increased convenience and ease of use with the potential to improve patient compliance – especially in certain patient populations.

IERs can be used to enhance the solubility and dissolution of poorly soluble drugs. In the case of poorly soluble ionizable drugs, the release of the API from a resinate can be faster than the rate of dissolution of the solid form of the drug. IERs provide a unique solution to control API release in tablets and liquid suspensions and can be combined with other excipients to provide targeted release profiles.

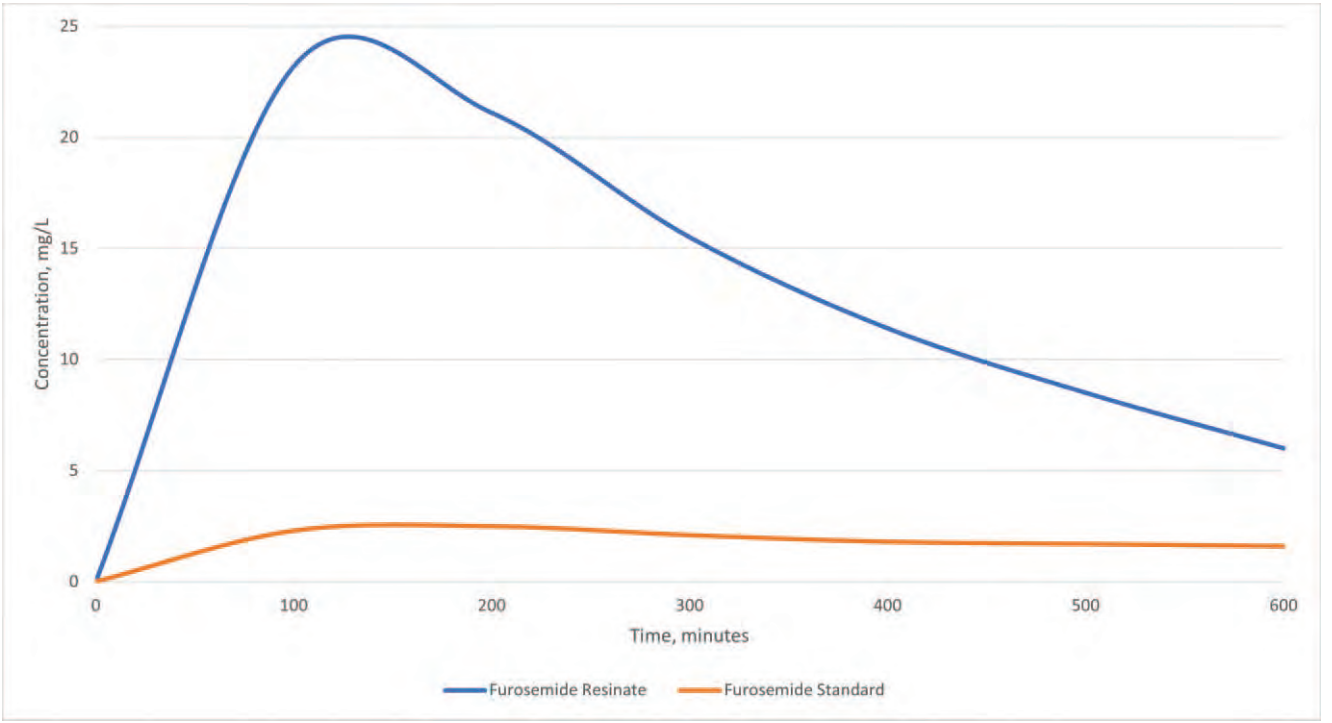
In addition, a drug's efficiency depends on the speed at which the tablet disintegrates in the stomach. IERs that swell easily in an aqueous medium can rapidly disintegrate the tablet by creating internal pressure. Certain IERs show a minimal adherence rate, and therefore are more effective for such formulations. When looking at the release characteristics of the furosemide standard alone, it has very poor solubility, so no bioavailability of this material is seen. But when loaded onto a resinate, there is a higher payload of amorphous drug from the formulation.

HELPING PATIENTS OF THE FUTURE

With oral formulations making up the majority of drugs on the pharmaceutical market, more effort is needed to enable certain patient groups to take advantage of the benefits they provide. To do this, alternatives to solid tablets and capsules must be a focus for drug manufacturers whether that be liquids and syrups or ODTs and chewable gummies. While these circumvent issues with swallowing, they pose more problems due to the bitter taste that they can carry.

To overcome these problems, IERs should always be considered as an integral part of a formulator's armament in the dosage form design. Companies can use these resins to tailor products to the

FIGURE 2



FloVitro results for 80-mg dose of furosemide standard versus furosemide resinate. The resinate was created using DuPont™ Duolite™ AP143/1083. The furosemide drug was loaded onto the resin at a 30% weight.

needs of specific segments of the population, in particular, the pediatric and fast-growing older populations of patients or create more convenient dosage forms. IERs solve various pharmaceutical formulation issues, including decreasing the bitter taste of many pharmaceutical drugs, improving patient outcomes by supporting compliance to treatment regimens, and providing new revenue streams for pharmaceutical companies.

The use of IERs can be a win for patients and the pharmaceutical industry. They can help improve the manufacture of drugs to deliver solutions that result in better outcomes for patients and life science companies alike.

AUTHOR'S NOTE

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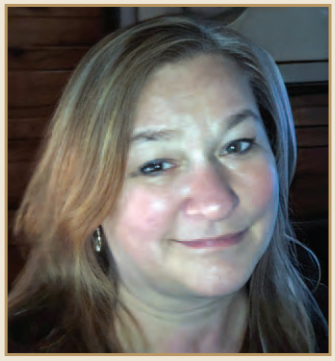

Amie Gehris earned her degree in Biology from Edinboro State University, PA, US. Since then, her career has spanned The Rohm and Haas Company, The Dow Chemical Company, and now DuPont. Since 1999, she has supported pharmaceuticals and bioprocessing in R&D roles, quality control, technical support, and application development. Currently, she is the Key Account Manager for the Life Sciences and Specialty business in DuPont in North America. In addition, she's the Technical Service Manager for Ion Exchange Excipients and is the Subject Matter Expert (SME) for AmberLite™ and Duolite™ ion exchange resins globally.

DELIVERY DEVICES

Growing Connected Market Set to Elevate Healthcare Outcomes

By: Michael Earl

INTRODUCTION

The market for connected drug delivery devices is projected to grow by as much as 23.4% each year between 2022 and 2030, with the value of the category expected to reach $25.6 billion by 2030.[1] This rapid expansion is being fuelled by trends both within and outside the healthcare sector: the increased adoption of the Internet of Things (IoT) through smarter devices with sophisticated sensors and processing ability; a growing recognition that enabling contactless health services strengthens efficiency (further reinforced by the Covid-19 pandemic); and the trend toward smarter consumer devices tracking health metrics.[2]

Introducing digital features to medical products is a logical step in light of these trends, but there are also commercial and healthcare incentives. As the industry continues to grow and develop, the following examines what the connected device market will look to achieve in the coming years and how it is likely to drive improved adherence to treatments and improve overall healthcare outcomes.

STRENGTHENED PATIENT SUPPORT

Given the current trends in drug development, developing drug delivery devices that provide users with detailed instructions for each step of the injection experience is particularly important. As well as an increase in the move from intravenous to subcutaneous administration, drug formulations are changing as companies look to minimize disruption to patients' lives by increasing the time between injections. Some extended-release formulations allow patients to go much longer between treatments, in some instances up to 6 months. With patients using devices less frequently, there is a greater need for clear guidance during the injection process.

Connected devices can provide real-time, in-use feedback to patients to guide them through each step of using the device. This helps reduce the risk of errors in the injection process during self-administration, which could lead to a failed or incomplete dosage. Additionally, training devices, with enhanced sensors allowing specific and individualized guidance to those using a device for the first time, can also help to increase patient confidence and successful administration. They may also be a reassuring support tool for those switching devices.

In addition to the guidance patients receive from their device, the collection of injection data is set to become a simpler process for patients. Currently, most connected devices are accompanied by a smartphone app that must be downloaded for access to device data such as injection reminders. However, with the emergence of 5G, we will increasingly see device data directly uploaded to the cloud without the need for secondary apps or devices. This will enable real-time data transfer, allowing healthcare professionals to monitor treatment remotely without the need for any input from patients. Apps are likely to take on a secondary role with data transferred from the cloud back to the apps for patients to view if they wish.

With the emergence of 5G, we will increasingly see device data directly uploaded to the cloud without the need for secondary apps or devices.

A HOLISTIC VIEW OF PATIENT HEALTH

A plethora of data can be captured and stored by connected drug delivery devices, such as detailed real-time data about injection date, time, dose, and injection site as well as confirmation of the drug and expiry date. These could be combined with other data sources to provide a holistic view of patient health and to better understand their specific treatment needs. Both physiological data – such as blood pressure and heart rate – and lifestyle data around sleep and exercise habits are now easily captured and consistently monitored due to wearable devices such as smart watches. In the future, using information collected from these consumer products in conjunction with data from drug delivery devices could be invaluable in triggering the necessary patient interventions and ultimately improving healthcare outcomes.

In healthcare settings, what we have seen so far is limited interoperability – the ability of computer systems or software to exchange and make use of information – and data integration. This is beginning to change due to the increasing focus on remote patient monitoring. Providers are seeing the benefits integrating data can bring in terms of healthcare outcomes.[3] As a fuller picture of a patient is developed through multiple data sources, healthcare professionals ideally would be able to develop optimal treatments or treatment regimens tailored to each patient. This in turn is likely to increase adherence to treatment plans, create an overall healthier population, and thereby reduce financial strain on payors and healthcare systems.

BETTER PERFORMING DEVICES

Key data about how patients are using a device – for instance, the angle at which the device is being held or the amount of force applied – could also be collected during the clinical trials phase by using connected devices. This can then be used to support data gathered during human factors studies – providing evidence that patients are using devices as intended during clinical trials. Post launch, the data can be useful in identifying and resolving any user issues, as well as enabling root cause analysis. This information can also be passed onto the device manufacturer who can work on usability issues and determine if design changes may be necessary for certain patient groups. This means the data collected from connected drug delivery devices over time will play a critical role in improving the device itself, and ultimately providing an optimized experience for patients.

GREATER DEVICE OPTIONS FOR PHARMA COMPANIES

With the connected device market evolving rapidly and numerous manufacturers looking to be part of it, there is a increasing list of device designs and configurations for pharmaceutical compa-

Key data about how patients are using a device – for instance, the angle at which the device is being held or the amount of force applied – could also be collected during the clinical trials phase by using connected devices.

nies and patients to choose from – spanning from single-use and reusable devices to integrated or add-on connectivity. Opinions on the best options are constantly changing as wireless technology and the performance of different electronic components continue to evolve. Commercial arguments are also shifting as regulations evolve rapidly and sustainability considerations grow in importance. With significant differences in regulatory approval pathways and environmental standards, the best options in one market may not necessarily work for another.

Due to this myriad of changing factors, pharma companies are understandably looking for flexible drug device platforms. Devices that can accommodate different fill volumes – for instance, through innovations such as self-adjusting plungers – are understandably more attractive. Likewise, devices that can work with or without connectivity are useful to pharma companies, as they allow flexibility based on the preferences of a particular patient group, or the cost and reimbursement status in different healthcare markets. The ability to choose between single-use and reusable devices depending on therapy, market, and patient needs is also important for pharma companies looking for suitable device manufacturers. Going forward, these different avenues should lead to an array of different device options and features being developed – meaning more choice for both pharmaceutical companies and their patients.

SUMMARY

The growth in the connected drug delivery market in the coming years is likely to lead to improvements in a number of areas. Patients will have access to devices that are more intuitive and user friendly, helping them to be more confident during self-administration and improving the injection process. Moreover, the ability of devices to upload data directly to the cloud will help optimize the process of data collection, allowing for real-time data transfer without manual input from patients themselves. As more data is gathered on how patients are using devices and where issues are occurring, manufacturers will be able to modify devices to meet the needs of different patient groups. In turn, this will provide further options for patients who

are already beginning to benefit from the numerous options emerging from a growing connected drug delivery device market. ◆

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Michael Earl joined Owen Mumford as Director of Pharmaceutical Services in November 2020. He was previously the Commercial VP at Bespak, leading the commercial team there to drive growth in their substantial medical devices business. Prior to that, he worked for several pharma, biotech, and device companies. In a career spanning more than 35 years, he has been responsible for all aspects and stages of drug and device development and commercialization. He has also completed a substantial number of commercial, licensing, and M&A transactions.

Drug Development
EXECUTIVE

Denis Dufrane, MD, PhD

CEO & Founder

Novadip Biosciences

Novadip Biosciences: Developing a New Class of Regenerative Tissue Products to Accelerate Healing of Critical Size Bone Defects, Trauma & Spinal Problems

Novadip Biosciences is a clinical-stage biopharmaceutical company leveraging its proprietary 3M^3 tissue regeneration technology platform to generate multiple product candidates to address tissue reconstruction. Using its unique 3M^3 platform to drive multiple product classes, Novadip's mission is to provide innovative solutions for patients who have limited to no treatment options. *Drug Development & Delivery* recently interviewed Denis Dufrane, MD, PhD, Chief Executive Officer, and Founder of Novadip Biosciences, to discuss the company's innovative approach to tissue regeneration technology.

Q: What problem is Novadip looking to solve with its unique 3M^3 tissue regeneration technology platform?

A: Novadip is committed to changing lives by providing innovative regenerative medicine solutions for patients with limited or no effective treatment options. Our team is focused on accelerated healing and single curative treatments for large bone defects, bone non-union, and spine fusion.

We are also using this platform to manufacture highly specific and reproducible cell-free microRNAs/exosomes that can regenerate hard and soft tissue following surgical resection and which also has shown intriguing evidence of anti-cancer activity. The program has the potential to address a variety of solid tumors, such as osteosarcoma, melanoma, and glioblastoma as well as metastatic disease.

Q: What is Novadip's 3M3 platform technology?

A: The 3M³ technology platform consists of a 3-dimensional, scaffold-free, extracellular matrix (ECM) utilizing differentiated adipose-derived stem cells (ASCs), to generate highly specific growth factors and miRNAs to restore the physiology of natural healing.

The technology is based on adipose-derived stem cells, which are easily harvested from the patient's or donor's fatty tissue and, when differentiated, have superior osteogenic properties compared to bone marrow-derived stem cells. The platform generates a continuous cycle in which active particles are combined with the differentiated ASCs to produce an extra cellular matrix containing a cocktail of bioactive ASCs, highly specific miRNA, growth factors, and proteins, all of which work together to promote accelerated stable tissue regeneration.

Our 3M³ platform drives multiple classes of product candidates, including autologous cell-based therapies for critical size tissue reconstruction, allogeneic ASC-derived therapeutics for use in prevalent bone grafting procedures and solid tumors, and miRNA/exosome and matrisome-based therapeutics for treatment of solid tumors.

Q: What drug candidates are in the Novadip pipeline that will be delivered with these platforms?

A: Novadip's lead asset, NVD-003, is an autologous therapy derived from adipose stem cells that has the potential to provide a single treatment cure to save limbs and restore mobility in patients with congenital pseudoarthrosis of the tibia (CPT), a rare pediatric bone condition characterized by fractures of the shin that fail to heal properly. Occurring in 1 of 150,000 births, CPT patients are at high risk of tibial fracture and face a lifetime of pain, limited mobility and potential amputation. Current treatments involve intensive surgery to try to join the bone and patient may still face amputation despite enduring years of conventional treatment.

While there are a number of commercially available and investigational products intended to treat smaller bone defects, NVD 003 is the only product in development to treat large bone defects. It has a rare disease designation from the FDA and, if approved in the US, Novadip becomes eligible to receive a priority review voucher from the FDA worth up to $10 million. This provides an accelerated development and regulatory pathway and confers market exclusivity in the estimated €500 million ($509 million) CPT market. The company has initiated a Phase 1b/2a clinical trial to study NVD-003 in a total of CPT patients between 2 and 8 years of age in the US and EU.

The company is also developing an allogeneic "off-the-shelf" therapeutic, NVD-X3, to provide accelerated, durable bone union in common orthopedic conditions, such as spinal fusion and non-healing fractures. Using adipose-derived stem cells developed in an acellular matrix, NVD-X3 has the potential to effectively regenerate bone and soft tissue without inducing immunogenicity or GvHD.

As an allogeneic therapy, NVD-X3 has a favorable cost profile that can allow broad distribution and expanded access for patients undergoing spinal fusion or suffering from recalcitrant non-healing fractures. This is a very large market opportunity in the $7-billion bone substitution market. Preclinical studies demonstrate that NVD-X3 offers superior bioactivity without the undesirable bone formation/resorption and inflammation observed with currently marketed bone engraftment products. Novadip plans to initiate a Phase 1/2 clinical trial in Europe in early 2023 for NVD-X3 in spine fusion and bone non-union procedures, which account for 60%-70% of the bone graft market.

We are applying our 3M³ technology platform to generate large quantities of purified and highly specific miRNAs/exosomes for the treatment of solid tumors. We have identified several miRNAs involved in the modulation of bone remodeling, inhibition of cellular proliferation, and tumor development. Potential indications include systemic tissue diseases, such as osteoporosis and osteoarthritis, as well as certain solid tumors.

We have identified a lead candidate, NVD-M2, that we plan to advance into human clinical trials for the treatment of solid tumors, such as osteosarcoma, glioblastoma, and metastatic disease, in 2024.

Q: How will this novel drug delivery technology impact patients?

A: Patients with critical size bone defects and bone non-union from trauma often face years of invasive surgery, permanent loss of mobility, and even amputation. The FDA defines a bone non-union as a fracture that is at least 9 months old and has not shown any signs of healing for 3 consecutive months despite surgical intervention.

We are working to develop a new class of regenerative

tissue products that mimic the natural physiological process of bone formation to accelerate healing of large bone defects, bone non-union, and spinal fusion in a single treatment. Our therapies have the potential to give these patients a chance at living a normal life.

For example, in a Phase 1/2 pilot study, our autologous product NVD-003 was applied in nine patients with bone non-union of the lower limb from trauma, who had previously undergone several surgical procedures; in one case, a patient had undergone 14 previous procedures. Two-year clinical and radiological follow up confirmed NVD-003 achieved stable and irreversible bone healing in patients with recalcitrant bone non-union in the lower limb following failure of conventional surgical and bone engraftment treatments. Rapid bone formation was confirmed at 3 months post-implantation in all patients. The median and mean time to clinical healing were 6 months and 9 months post-implantation, respectively.

Q: What do you see as the biggest opportunity for Novadip to change the treatment paradigm for patients?

A: The results we have seen from treating more than 50 patients in clinical trials or in compassionate use suggest that 3M³-derived therapeutics could eventually replace current first-line treatments for critical size bone defects and common orthopedic procedures such as bone non-union and spinal fusion.

Overall NVD-X3 has potential clinical utility in more than 90% of the 1.6 million bone grafting procedures performed each year. By comparison, Medtronics' Infuse® product covers 43% of this market (30% of these procedures use Infuse off label).

Q: Looking ahead, what is your ultimate goal for Novadip?

A: Our goal is to help patients achieve accelerated healing so they can return to a normal, active life as quickly as possible. Many of our target patient populations, whether little children with CPT or people who have suffered from severe trauma, face a lifetime of disability, pain, repetitive surgeries, and even amputation. We have developed a technology platform that will yield multiple therapeutic products that can help advance the standard of care in orthopedic medicine and oncology – in many cases by providing a single treatment cure for patients who have no other treatment options. ◆

DRUG-ELUTING SYSTEMS

Introducing Drugs to Silicone & Controlling Elution Rates

By: Zach Fletcher

INTRODUCTION

Implantable drug delivery systems have the potential to address some of the biggest challenges patients face today. Through continued development of these technologies, many patients living with chronic conditions can realize significant improvement in their overall quality of life. Therapy developers who embrace drug elution technologies are uniquely equipped to solve patient compliance and drug side effect challenges, while also having the greatest capacity to provide extended-release dosages to the market.

In addition, introducing Active Pharmaceutical Ingredients (APIs) can improve the efficacy of medical devices. Through similar manufacturing methods, application of APIs can combat inflammation and/or fight microbial risks around a procedure site.

To maximize the potential impact of these technologies, manufacturing processes must continue to evolve as the desired number of drug compounds used in these forms rises. Most existing drug compounds exhibit various sensitivities that cause them to break down when using established manufacturing methods. Because of this, it is critical for therapeutics manufacturers to understand the methods in use today and continue improving processes.

MARKET OUTLOOK

Pharmaceuticals

Because of all the aforementioned advantages, the growth forecast for the global implantable drug delivery device market is 10% annually in the coming years with an expectation to rise to nearly $30 billion by 2025.[1] Contraceptive, ophthalmic, cardiovascular, diabetes, oncology, and autoimmune disease applications are all likely to focus on development of these therapeutic forms.

Medical Devices

Meanwhile, the drug/device combination product market is projected to grow at nearly 9% each year, starting with an estimate of the 2021 market of $118.[1] billion. By 2026, this figure looks to rise beyond $180 billion, driven by the demand for transdermal patches, drug-eluting stents, wound care products, and antimicrobial catheter applications.[2]

EARLY USES OF THE TECHNOLOGY

Given the potential of the pharmaceutical and medical device markets, there are significant opportunities for the advancement of drug-eluting therapy and its applications. Some of the earliest products, defined as single-entity combination products, focused on the application of anti-inflammatories and anti-microbials in medical devices. The application of these drug compounds allows for the increased efficacy of stents and balloons used to treat coronary heart disease. These early systems are examples of a medical device acting as the Primary Mode of Action (PMOA) for therapy.

Alternatively, products such as implantable contraceptive products and intrauterine systems are examples of the same drug-eluting technologies in which the drug is the PMOA.

ADVANTAGES OF DRUG-ELUTING SYSTEMS

Applying anti-inflammatories and anti-microbials continues to be a viable method for improving the efficacy of medical devices or providing additional therapy to supplement the effect a device has on a patient. The greatest potential impact drug-eluting technologies can have is on drug delivery. Formulation of implantable systems make it possible for patients to receive a one-time dosage of a therapy, while minimizing the day-to-day demand to monitor their condition.

In scenarios in which patient compliance is paramount, drugs delivered via implantable systems give patients options to move from once-daily oral dosage forms to a single implantable dosage that provides several months or years of therapy. In addition, these systems can provide targeted delivery within the body to avoid systemic administration of the drug, which commonly drives the need for higher dosages. Finally, localized delivery and lower dosages may allow for significant reduction in patient side effects from taking a specific therapeutic.

APPLICATIONS TODAY & IN THE FUTURE

Many of the previously mentioned therapeutics will continue to evolve as technology improves. Beyond enhanced medical devices and contraceptive products, there are other applications in which these therapeutic systems are growing. Ocular systems are a major focus area for drug-eluting systems because of the inefficiencies and patient non-compliance concerning eye drops. Additionally, oncology has seen advancements in drug-elution due to the advantages targeted delivery presents for chemotherapy drugs. Finally, HIV/AIDS, diabetes, anti-psychotics, addiction deterrence drugs, and some animal health applications are pursuing extended-release solutions that may progress to implantable systems.

EXCIPIENT MATERIALS & MANUFACTURING PROCESSES

There are many specific materials used in drug-eluting systems, and these can be classified as either biodurable or bioresorbable polymers. Depending on variables, such as the intended drug-release window, the melting point of the therapeutic, and compatibility of the drug with different excipient material, the ideal polymeric excipient can vary for each therapeutic.

Another factor to consider are the advantages to a specific design for the system. Some formulations carry no specific physical design requirements and can be optimized for high volumes while cutting

An extruded or molded rod is a common form for a polymeric drug delivery vehicle.

out costs. However, other systems may benefit from a specific geometry to deliver the drug effectively. Lastly, there may be situations in which the release of the drug from the system needs to be modified to achieve the desired rate of elution for therapeutic effect. Because of these complexities, it's beneficial for therapeutic manufacturers to have a component partner with a diverse set of manufacturing skills and processes including:

- **Extrusion** – Most common for high-volume drug delivery
- **Molding** – The best process for customized geometries
- **Sheeting** – Suitable when additional surface area provides advantages, and a burst release effect is ideal

FORMULATION METHODS

Beyond how to get the excipient polymer into its final form, drug-eluting application experts must consider when to introduce the drug into the system during manufacturing. Drug compounds with low melting points may break if exposed to certain temperatures during the manufacturing process. In addition, the chemistry of other drug compounds may inhibit the curing process. These considerations, along with desired changes to the rate of elution may influence the development of the manufacturing process.

Mix & Manufacture - The most commonly used process in which both the drug compound and excipient materials are mixed prior to manufacturing.

Immerse & Impregnate - The introduction of the drug to the system after completion of the manufacturing process. This allows for successful introduction of the drug while avoiding the heat-intensive steps involved in most manufacturing processes.

Membrane Application - Used in situations where a solid drug core can be enclosed behind an effective membrane. This can effectively control the release profile and proves effective if the originally designed system is exhibiting a faster release rate than desired.

SUMMARY

Implantable drug delivery systems are an emerging drug delivery form and will continue to build momentum in the future through the advantages they provide to patients across numerous applications. An experienced manufacturing partner can help therapy developers quickly identify solutions and develop manufacturing and formulation methods for use in many applications. ◆

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BIOGRAPHY

Zach Fletcher is Trelleborg Healthcare & Medical's Business Development Manager for Polymeric Drug Delivery. Having spent nearly a decade in manufactured medical devices, he now focuses on implantable drug delivery systems, combining his knowledge of the market with his team's expertise in multiple formulation techniques to combine drug and polymers. A graduate of the University of Wisconsin – Eau Claire, he is excited to see how long-acting drug delivery platforms impact on patient lives in the future.

Special Feature

Parenteral Drug Delivery: Could a Dose of AI Improve Development?

By: Cindy H. Dubin, Contributor

Elon Musk just warned the world that Artificial Intelligence (AI) is dangerous and has the potential to destroy civilization. Yet, AI will likely be used in nearly every industry, and the biopharma industry is no exception. A new report from VisionGain[1] shows that 75% of pharmaceutical organizations want to use automated solutions more frequently, driven by injectable drug delivery. The report found that pharmaceutical production lines are challenged by customized dosages and products such as prefilled syringes (PFS). Therefore, manufacturers are searching for equipment that can handle the greater range of formats generated in smaller batch sizes, while still reducing downtime. Additionally, the popularity of injectables has increased the focus on sterility and product safety, an area where experts see AI having an impact.

While the industry is just at the precipice of discovering what AI can do for injectable delivery, this exclusive *Drug Development & Delivery* annual report highlights the strides that companies are currently making toward improving dose accuracy, integrating design safety, and accelerating time to market.

Owen Mumford's UniSafe® 2.25mL spring-free passive safety device for prefilled syringes.

Aenova: Filling Line With ±1% Dosage Accuracy

Over the past two years, more than $22 million have been invested in Aenova's Latina site to offer customers modern, Annex 1-compliant, aseptic filling technology for sterile dosage forms, especially vials and PFS. This new manufacturing area has been approved by the Italian authority (AIFA). Follow-on investments of approximately $16 million are currently underway to further expand the offering.

"The prefilled syringes segment is indeed increasing for the usage of controlled drug delivery devices on targeted therapies, such as monoclonal antibodies and cell and gene therapies," says Paolo Abbate, Managing Director, Aenova Latina Site. "Moreover, the request is always combined with a need for high dosage accuracy. Aenova, a CDMO, can offer a high performance line with ±1% dosage accuracy."

The Latina site also features a visual inspection system to assure that the product delivered to the patient is of the highest quality and that defects are minimized. "Fully automated filling lines under Restricted Access Barrier Systems (RABS), or Isolation, significantly reduce the risk of both breakages and contamination," he says. "Aenova is currently performing extensive assessment of the packaging equipment on the market to ensure that we remain at the forefront of technology to further reduce secondary and tertiary packaging defects."

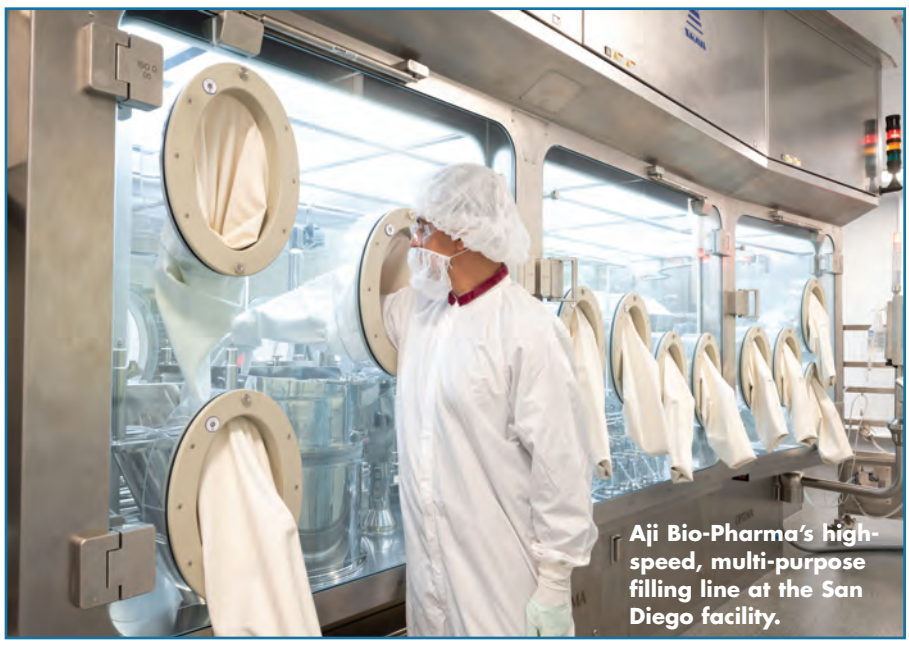
The Aenova Site Latina offers manufacturing services to a global market for both clinical trials material manufacturing and commercial supply. A new filling line can support batches from 10L to 1,500L, working with both disposable and stainless steel equipment trains. "Technology transfer activities and the PPQ strategy are established in agreement with customers and are fully compliant with cGMP guidelines," says Mr. Abbate. And quality control supports in-process control, product release, and stability testing, while also providing a comprehensive service for microbiological and chemical testing.

Ajinomoto Bio-Pharma Services: Flexible Services From Early Clinical to Commercial

Ajinomoto Bio-Pharma Services is a CDMO with six automated aseptic fill lines that have the capability to fill early-clinical through commercial products in vials, syringes, and cartridges. With the increase in demand for biologics in the market, Aji Bio-Pharma has technical experts with the experience to meet the unique needs of these products. "We also pride ourselves on being one of the few CDMOs with complex formulation expertise that includes a strong formulation team with extensive knowledge to help guide clients when manufacturing lipid nanoparticle (LNP) products," says Jennifer Etchison, Sr. Director of Business Development, Aji Bio-Pharma US.

As a mid-sized CDMO, Aji Bio-Pharma is flexible to cater to all product life-cycle phases. "For early-phase projects, we have capabilities to fill small batch sizes and manufacturing slots for quick turnaround times," she explains. "For late-phase/commercial projects, we have high-speed lines to accommodate larger batch sizes, scale-up, Process Performance Qualification protocol, and commercial experience."

In response to customer requests to increase batch size capabilities and accommodate larger commercial batches, Aji Bio-Pharma's San Diego site expanded aseptic filling capacity with a new high-speed multi-purpose filling line. This line is fully contained within an isolator and offers a range of configurations, including prefilled syringes, cartridges, and vials, and utilizes ready-to-use components to provide component and scheduling flexibility. And, to accelerate batch release and get client products to market sooner, the company has invested in automated and semi-automated visual inspection equipment.



Aji Bio-Pharma's high-speed, multi-purpose filling line at the San Diego facility.

ApiJect Systems: BFS Platform Addresses Safety & Supply Chain

ApiJect helps pharma companies improve delivery of liquid pharmaceuticals in customized, efficient, and scalable prefilled drug delivery systems. The ApiJect platform is a device design and manufacturing process that brings together the scale and economics of Blow-Fill-Seal (BFS) aseptic filling with the simplicity of attachable plastic component design, such as needle hubs, to create simple, prefilled injectors. Additionally, ApiJect devices can be designed with safety features, such as needle shields and auto-disable mechanisms, as well as single-dose packaging.

"Whether it is a high-value injectable treatment for a small number of patients or an essential vaccine for the world, ApiJect helps pharma companies deliver more of their injectables to the patients who need them," says Tony Wasilewski, MPD2, PMP, Vice President, Pharmaceutical Development Services, ApiJect Systems.

He explains BFS is more compact and requires fewer raw materials than traditional glass filling lines or traditional prefilled syringes. This, he says, has become a key factor as companies consider supply chain shortages. "Rather than glass, we embrace pharmaceutical-grade resin to create almost our entire device, with the exception of the hypodermic needle," says Mr. Wasilewski. "Better control over the materials, a less complex supply chain, and the use of resin instead of glass allow devices packaged in BFS to reduce or eliminate many of the hazards that can lead to product recalls from packaging."

While ApiJect drug delivery systems are still in development and have not been cleared by the FDA or other regulators, ApiJect is working with several pharma partners to develop ApiJect prefilled injectors for their injectables. He says: "The potential of our platform is what led to our development agreement with global contract manufacturer, Fareva. With the support of the French Government, Fareva is building three new BFS lines in France with ApiJect technology to fill-finish vaccines in ApiJect prefilled injectors."

Aptar Pharma: ETFE Film-Coated Syringe Plungers Protect Sensitive Injectables

Sensitive drugs and biologics require additional protection from filling to the point of administration. Choosing the right primary packaging for these drugs is critical, and manufacturers must ensure that their syringe and components protect the drugs without compromising on key functional performance such as gliding force, break-loose force, container closure integrity, and machinability.

Ethylene Tetrafluoroethylene (ETFE) film-coated closure components are now commonly used for packaging sensitive vaccines and biologics. "ETFE film-coating possesses excellent chemical resistance and has been proven to act as a barrier that protects the drug from extractables and leachables and the potential threat they present to the integrity of the drug formulation," says Audrey Chardonnet, Director of Business Development for Prefilled Syringe Components, Aptar Pharma.

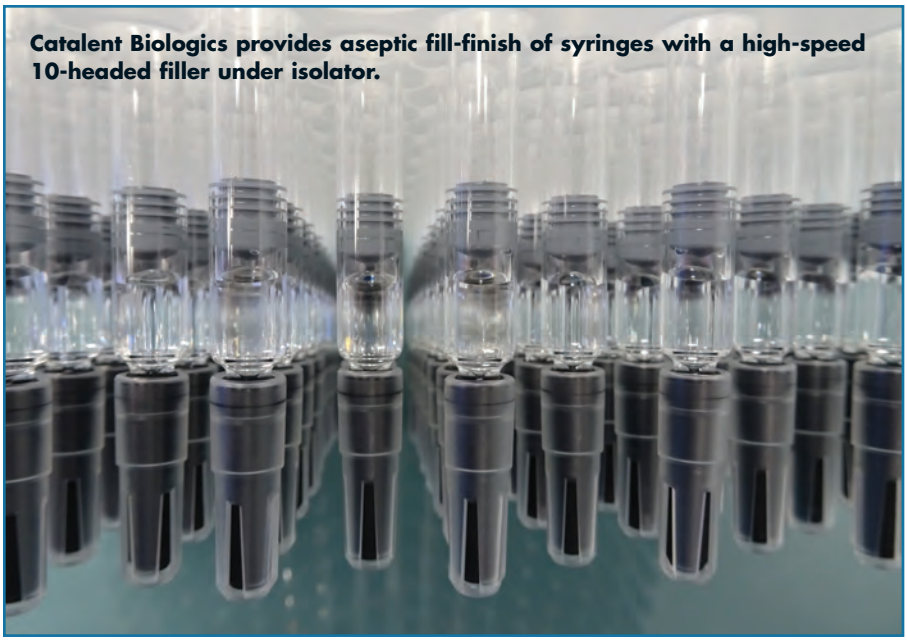
While ETFE film-coated components are an effective solution for packaging sensitive drugs, they are not without their challenges. To date, compatibility with vent tube filling methods and achieving consistent functional performances remain key unmet needs when using ETFE-coated syringe plungers, she says. As a result, Aptar Pharma has developed new designs of coated syringe plunger to promote machinability, container closure integrity, and functional performances.

Aptar Pharma uses a proprietary 3-rib design for its ETFE-coated solution, PremiumCoat®, with the trim rib specifically positioned to avoid interference with functionality. Because the three ribs come in contact with the glass, compared to the market standards, PremiumCoat has demonstrated its capacity to preserve container closure integrity, even in deep-cold storage conditions. This design was also shown to enable low and consistent gliding and break-loose forces, which facilitates the development of autoinjectors. Aptar Pharma also performed a series of machinability testing to demonstrate that PremiumCoat is compatible with vacuum and high-speed vent tube filling lines.

"With Aptar Pharma's 3-rib PremiumCoat design, manufacturers can reconcile ETFE coating with machinability, container closure integrity, and functional performance, providing superior protection for sensitive drugs, optimizing operations on their filling lines, and ensuring safety for their patients," says Ms. Chardonnet.

Catalent Biologics: Simplifying Tech Transfer to Accelerate Programs

Pharma companies developing new injectable medicines are aiming to meet more patient needs. This is evident with the development of new off-the-shelf autoinjectors that can administer larger volumes of drug product (e.g., 5mL). To meet this demand, CDMOs such as Catalent are adding more high-speed, state-of-the-art assembly solutions, which are able to accommodate these innovative devices.



Catalent Biologics provides aseptic fill-finish of syringes with a high-speed 10-headed filler under isolator.

Catalent Biologics' drug product facilities in North America and Europe provide integrated solutions for customers developing new biological entities, biosimilars, and sterile injectables. These include early-phase development and manufacturing to late-phase commercial fill-finish and packaging.

"We work to simplify the tech transfer of products between the company's early-phase facilities and late-phase/commercial facilities, which reduces risk, and accelerates programs through the clinic and to market," says Brian Galliher, Principal, Process Engineer, Catalent Biologics.

"Robust tech transfer processes also help to ensure that risks are minimized, and equipment selection is critical (e.g., single use system compatibility, filling and packaging/assembly equipment) along with thorough qualification programs such as line handling studies, engineering runs, container closure studies with container closure integrity testing (CCIT)."

Catalent continues to see growth in the prefilled syringe market. COVID-19 vaccines, for example, are moving away from the multi-dose vials and into single-dose syringes (and single-dose vials), and new treatments to reduce obesity are focused on at-home patient administration. These are following the trend to include prefilled syringes and autoinjectors for both the ease of use and patient adherence reasons, says Mr. Galliher.

A customer of Catalent initially launched its product in a 1mL-long syringe, which required the patient to administer two doses for one treatment, and was not the ideal situation. In parallel, Catalent qualified a 2.25mL format in primary and secondary packaging, including an autoinjector assembly. For the patient, this new format has the potential to reduce the number of injections per treatment, and the use of an autoinjector provides benefits of ease of use and safety.

Congruence: Autoinjector Could Mitigate Premature Removal

Several trends are driving the need to inject high-dose biologics into the subcutaneous (SC) tissue. But high viscosity (25-150^{+}cP) and higher injection volumes associated with high-dose drugs challenge the limits of what is feasible with legacy spring-powered autoinjectors due to high injection forces required.

"Tradeoffs are imminent when accepting spring-powered autoinjector size for high-dose biologics either by needing to use a large device and/or long injection times, both of which impact patient experience and comfort," says Gautam Shetty, PhD, Congruence. "Designing an autoinjector for high-dose drugs is not simply a scaling problem (i.e., making existing autoinjectors bigger). Hence, alternate – compact yet powerful – energy sources in an autoinjector or new technology platforms, such as wearable injectors, are being pursued."

He adds that administering high-dose drugs with conventional spring-based autoinjectors is limited by low flow rate and long injection times because of insufficient force for faster delivery. There is a risk that cold temperature, when the drug viscosity is even higher, could render the autoinjector incapable of injecting, which would result in a missed or lost dose. Therefore, an autoinjector should provide sufficient force to operate even when an injection is attempted immediately after removal from a refrigerator.

Even though autoinjectors have been widely used, usability shortcomings have always existed. One such example is premature removal of the autoinjector prior to dose completion.

"Congruence user studies and published literature indicate that pushing the autoinjector against the injection site and holding it for an extended time is not obvious," says Dr. Shetty. "This problem is amplified with high-dose biologics, which would need longer injection times. User fatigue, exacerbated by longer injection times, could also cause premature removal of an autoinjector from the injection site."

Current autoinjector designs do not provide a safety net against premature removal. Once injection is initiated, current autoinjectors continue to dispense the drug even if the autoinjector is prematurely removed from the injection site, claims Dr. Shetty. And the safety shield locks, preventing the patient from resuming the injection. This results in an incomplete dose and potential non-compliance with therapy.

Another important consideration is that the pipeline of high-dose biologics includes patient populations with no history of self-administration using an autoinjector, such as patients with non-chronic conditions. Therefore, traditional risk mitigation strategies could potentially be irrelevant, says Dr. Shetty.

"The Congruence High Dose Autoinjector addresses high injection force need by incorporating a compressed gas source and addresses the usability issue of premature removal from the injection site by offering an Injection Pause™ feature," says Dr. Shetty. "This feature ensures that the injection is paused, should the autoinjector be inadvertently (or deliberately) removed from the injection site."

Credence MedSystems, Inc.: Dual-Chamber Syringes Suited for Varied Applications

Growth in the demand for dual-chamber prefilled syringes is being driven by multiple factors in the injectable pharmaceutical market. The delivery of medications is rapidly moving outside of the formal healthcare system and injections are being performed by more naïve users. The complexity of injectable drug products is growing, requiring separation of drug components during storage, despite efforts to achieve liquid-stable formulation. Pharmaceutical manufacturers are looking to drive cost and time efficiencies in their development pathways. Regulatory authorities desire clinical trials to be performed in the delivery system that will be used commercially. Emerging biotechs seek greater value by developing their novel therapies in enabling delivery systems.

"These factors have created pent-up demand for a user-friendly, effective, and safe delivery system for those drug products that require separation during storage," says John Merhige, Chief Commercial Officer, Credence MedSystems, Inc.

To satisfy this need, advances in technology are emerging both in the development of dual-chamber delivery systems as well as in the fill-finish processing of those devices. "It is not surprising that collaboration between device manufacturers and drug manufacturers is required to unlock the full potential of dual-chamber systems, the quintessential example of a drug-device combination product," he adds.

Credence MedSystems is developing its family of Dual Chamber Syringe products to meet the varied needs of these applications. The platform's flexibility is highlighted by the ability to turn any conventional barrel into a dual-chamber system that can allow either reconstitution or sequential delivery. In the area of reconstitution, the liquid can be mixed with a powder, lyophilized cake or another liquid before the reconstituted solution is injected. In sequential delivery, the two liquids are not mixed, but rather injected in sequence with one push of the plunger rod. Both configurations are available either with a needleless luer lock front end or with Credence's proprietary integrated needle-retraction technology.

"The passive needle retraction reduces the likelihood of needlestick injury, while integrating the needle-safety mechanism into the prefilled syringe eliminates capital and operating expense associated with conventional add-on safety devices," says Mr. Merhige. "Credence's Dual Chamber Syringes have fared extremely favorably in human factors evaluations as 'stand-alone' syringes, but can also be employed in conjunction with disposable or reusable autoinjectors."

One of Credence's collaboration partners advancing dual-chamber filling is Bryllan, LLC, a contract manufacturer of complex and novel drug products. Bryllan's existing filling capabilities, along with its plans for expansion, provide pharma innovative solutions in the manufacturing of ready-to-use systems, including dual-chamber syringes and bags. "With the ability to handle potent, toxic, and sensitive products, experience in both liquid and powder filling, and the expertise to build and operate highly flexible filling suites, Bryllan's advances are facilitating adoption for this field of drug delivery," Mr. Merhige says.

He adds that when paired with enabling fill-finish capabilities, Credence's Dual Chamber Syringes simplify administration of challenging drugs; reduce risks in the areas of accidental needlestick, dosing errors, contamination, and exposure to potent substances; and address economic factors by decreasing drug overfill and time of administration. He concludes: "These technological advances are addressing the trends in the market and providing value to patients, healthcare providers, and pharmaceutical manufacturers."

DALI Medical: Bringing Down the Cost of Integrated Safety Features

DALI Medical Devices offers a range of patient-centric injectable drug delivery devices that meet the need for enhanced

safety and ease-of-use, both for clinical trials and commercial drugs. The company also provides complete injectable drug delivery device development solutions that are customized for specific requirements relating to drug properties and user preferences, handling everything from concept to commercialization. DALI's portfolio offers solutions for liquid injectable drugs, drugs that need to be reconstituted, vials, prefilled syringes, etc.

Injectable drug delivery devices with integrated safety features do present various development and manufacturing challenges, often leading to higher costs compared to basic needles and syringes, explains Ziv Cahani, Vice President, Business Development, DALI. However, there are various strategies that can be implemented to simplify the manufacturing processes and supply chain, and bring down costs.

For example, DALI Medical offers safety needles and safety syringes that provide passive protection against needle stick injuries. With these devices, the safety features are activated automatically, without the user having to do anything.

"Although it's logical that the more advanced devices would be more costly to produce, strategies such as design-to-cost and design-to-manufacturability can make a huge difference in manufacturing costs," says Mr. Cahani. "By working closely with experts in injection molding, assembly automation, and raw materials selection, it is possible to offer highly advanced solutions with affordable pricing."

He recalls that one of DALI's customers was looking for a safety-enhanced delivery device for a super-high-viscosity drug. "We developed a version of our SAN®-Light passive safety needle, customizing it to meet the viscosity challenges and other requirements, including regulatory requirements and user preferences. The customized safety needle is tuned to the viscosity properties of the drug, provides a high level of safety, and incorporates features aimed at minimizing needle phobia anxiety as well as real and/or perceived pain."

Datwyler: Proprietary Coating Reduces Particulates

Datwyler's experience in rubber components has led to the development of NeoFlex™ plungers, a coated solution for prefilled syringes and cartridge-based delivery systems. Datwyler's proprietary spray coating technology provides a protective barrier to external contaminants, prohibiting leachables from entering the product and ensuring a contact-safe surface that is compatible with the drug, explains Paolo Ferrigno, Product Manager, Prefilled Syringes and Cartridges, Datwyler. "With our proprietary fluoropolymer coating technology and lack of need for silicone lubrication (under specific conditions), Datwyler contributes to a reduction in overall visible and subvisible particles."

The NeoFlex plunger production process is flexible to support the development of new products to optimize design according to customers' requirements and future life cycle management. "NeoFlex plungers have proven functionality in many plastic barrels, which are becoming more frequently requested for large containers to mitigate increased glass breakage risk," Mr. Ferrigno says.

Large-volume NeoFlex plungers are designed for self-injection devices. The increasing interest around self-injection devices has led to the development of solutions aimed at improving patient wellness and safety, the self-administration experience, and total cost reduction for authorities. The availability of new technologies and smart connection features allows for remote monitoring and reduces the risk of improper administration, incorrect dosage, and poor compliance.

In a PFS, a rubber closure is required to maintain sterility and needle integrity. For autoinjectors, a Rigid Needle Shield (RNS) seals the system, preventing contamination and preserving the sterility. The external plastic (polypropylene) shield is used to improve the mechanical interface with the autoinjector, allowing for a safer removal and eliminating the risk of tears or fails.

"For use in delivery systems, the functionality of the RNS needs to be proven both with the primary container (the syringe) and with the autoinjector," he says.

Datwyler provides RNS solutions in two sizes (1/2" and 5/8"), suitable for use in subcutaneous and intramuscular parenteral administration. "There is a clear trend to move from IV to subcutaneous/intramuscular administration, resulting in the development of large-volume delivery devices," says Mr. Ferrigno.

Datwyler's FM30 rubber compound is designed to allow ETO gas to penetrate, sterilize, and evacuate, while maintaining a low oxygen and water vapor transmission rate, Mr. Ferrigno explains. Different levels of siliconization are available to accommodate the pull-off force for a variety of syringe types.

INCOG Biopharma Services: Delivered Higher Yield & In-Line Weight Checks to Client

Leveraging 20-plus years of CDMO experience, and having supported manu-

facturing activities for more than 200 molecules, INCOG was designed and built as a new 90,000-sq. ft. facility to support drug product fill-finish manufacturing for biopharma companies. The facility is cGMP production ready, and is actively manufacturing commercial PPQ batches. There are currently 40 million units of installed annual capacity to fill vials, syringes or cartridges with an expansion in 2024 that will take capacity to over 140 million units per year. INCOG also offers services and support in development, QC, inspection/labeling/packaging, device assembly, stability studies, and storage.

INCOG was introduced to a biopharma company that was previously using a Tier 1 CDMO in the US to manufacture a commercially approved prefilled syringe. Cory Lewis, CEO, President, & Founder of INCOG, explains that this company shared its frustration with the customer experience it had been receiving from its existing CDMO.

"They experienced poor communication, delayed responses, and a lack of proactive updates related to the manufacturing of their commercial program that resulted in manufacturing challenges, low yield results, and excessive rejection rates from batches," he says. "The improvements that we offered to our customer included an unparalleled customer experience from contracting to technical transfer to batch manufacturing, as well as manufacturing benefits resulting in improved yield via line setup, and the 100% in-process weight checks integrated throughout the filling process."

Mr. Lewis adds that the customer was invited to INCOG to utilize the person-in-plant offices, demonstrating a commitment to the partnership. INCOG has begun manufacturing the PPQ batches and expects to host the FDA for the pre-approval inspection by early 2024.

"Our commitment to being customer-driven is what sets us apart from other CDMOs and gave our biopharma customer the confidence they needed to trust our company with their commercial prefilled syringe project," he says.

With a focus on PFS, Mr. Lewis says that while he sees a limited market presence of devices with integrated safety features, he believes that the industry will continue to respond to this challenge by leveraging emerging technologies and process innovations to streamline and optimize the manufacturing process. "Additionally, I expect that regulatory agencies will continue to drive demand for these products, placing increasing pressure on manufacturers to deliver safer and more reliable drug delivery solutions," he says.

He also sees industry taking action to address issues of breakages, leachability, defects in packaging, and contamination. "There will be a greater emphasis on design and engineering to ensure that prefilled syringes are robust, durable, and resistant to breakages and defects," he says. "There also will be a continued focus on materials science to identify and mitigate leachability and contamination risks. Finally, quality control and supply chain management will be improved to ensure that packaging defects are identified and addressed before products reach the market."

Lifecore Biomedical: Unique Challenges for Ophthalmic Customers

Lifecore Biomedical is a fully integrated CDMO offering expertise in complex aseptic formulation, aseptic filling into syringes and vials, and final packaging of injectable drugs and medical devices. Lifecore also manufactures pharmaceutical-grade, non-animal-sourced hyaluronic acid (HA) through a proprietary fermentation-based process.

Some of Lifecore's clients require high-gauge cannulas and needles for precision use in ophthalmic surgeries. "Due to high-viscosity formulations, injection pressure can increase the risk for needle detachment at the luer," says Kipling Thacker, PhD, Vice President & Chief Scientist at Lifecore. "In these cases, we have worked with our clients to implement needle-retention devices designed to prevent needle separation."

Ophthalmic drug and device manufacturers also need to comply with USP <789>, which defines testing parameters for particulates in solution. Dr. Thacker says the key to meeting the USP requirements is to avoid issues with particulates in all phases of production. "To address this issue, we have partnered with ready-to-use vendors on measures, such as the use of alternative syringe and vial materials, syringe cleaning, and improved component packaging. While the value of testing remains, asking the right questions up front and using a Quality-by-Design approach during development helps ensure a safe, consistent drug supply for patients."

Lubrizol Life Science – Health: Taking On Projects That Others Turn Away

Lubrizol Life Science – Health (LLS Health), CDMO Division, meets client demand for clinical trial material packaged in prefilled syringes by utilizing its Colanar Model FSM 1033. In this tub-based system, Lubrizol can fill PFS, cartridges, and essentially any primary packaging that fits in a tub, says Brett Braker, Engineering Supervisor, Technical Operations, LLS Health.

"This equipment offers us a lot of flex-

ibility to help our clients," he says. "Presently, we can fill 1-10mL syringes, but custom requests are feasible, and the system is particularly useful to fill smaller batch sizes that our clients seek. Larger, less flexible CDMOs, aren't willing to break into their productions to accommodate these requests. We, however, do not have a minimum batch size while having the capability to manufacture both aseptically processed and terminally sterilized material."

The consistency of filling accuracy and the bubble size in the cartridge helps reduce waste, which is important when working with high-value biologics and complex suspensions and emulsions. The filler operates using servo drives and a built-in peristaltic pump and bubble sizes are controlled using vacuum stoppering.

Most of the work LLS Health performs is for pharmaceutical clients seeking to increase the solubility and bioavailability of insoluble APIs or to improve long-acting drug products via the 505(b)(2) route. Recently, a large wearable device manufacturer asked the CDMO to perform some pre-clinical and clinical device validation work.

"When many larger, less flexible organizations had actually turned this client away, we leveraged the Colanar Model FSM 1033," explains Mr. Braker. "Working closely with the company, we provided both filled cartridges and fully assembled wearable devices. We made a range of material from 1 to 100 cP, helping them to define the limitations of their device for validation. Ultimately, we made both R&D and aseptically-filled cartridges for clinical use."

Mr. Braker says this partnership was a win-win for both companies. "Through helping the device manufacturer with their work, we learned more about our equipment, honing our ability to control the bubble size in the primary packaging, for example."

OXYCAPT™ Multilayer Plastic Vial & Syringe (Mitsubishi Gas Chemical Co.).

He adds that wearable devices, such as the one this client was developing, help patients maintain a more consistent level of the API in the blood. He says: "Wearable devices help with patient compliance and comfort as the devices often come prefilled, allowing them to dose themselves at home."

Mitsubishi Gas Chemical Co.: Multilayer Plastic Vials Are Ideal for Advanced Drugs

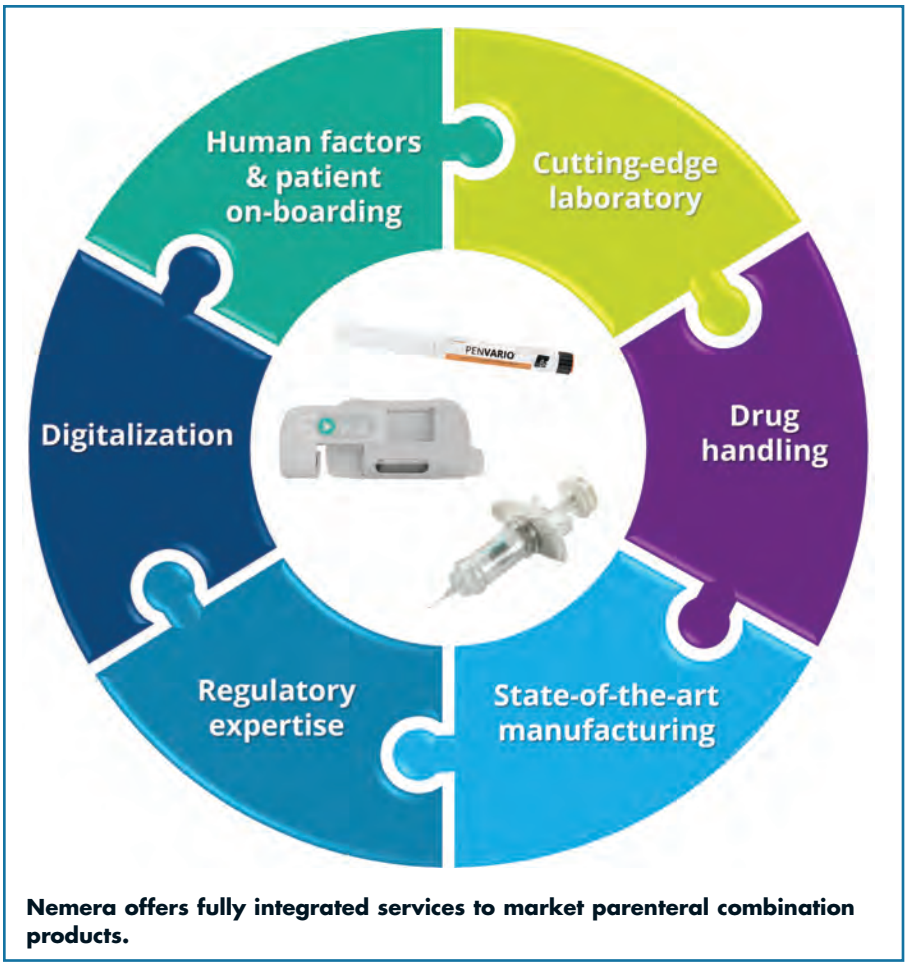
Mitsubishi Gas Company provides multilayer plastic vials, OXYCAPT, for the pharmaceutical industry. These products are often suited for biologics and cell and gene therapies stored at low or ultralow temperature. Plastic primary containers are expected to grow in popularity as companies consider storage for advanced drugs.

"As the compositions of advanced parenteral drugs have become more complex than existing drugs, we believe special and appropriate primary containers are required," says Tomohiro Suzuki, Associate General Manager, Mitsubishi Gas Chemical Company. "Special features, such as high pH resistance, low extractables, low protein adsorption, high break resistance at ultralow temperature, high oxygen barrier, high ultraviolet barrier, etc., are necessary for primary containers used for advanced drugs." He adds that multilayer plastic vials and syringes overcome breakage and leachability common with glass containers.

Mitsubishi Gas Chemical Company signed a Letter of Intent with Becton Dickinson (BD) in May 2022 and has started earnest discussions to apply its multilayer technology to next-generation PFS for biologics. "We believe this collaboration will be helpful for the pharmaceutical company to safely develop novel and sensitive future drugs," he says.

Nemera: Facilitating Combination Products' Sprint to Market

Nemera offers a range of parenteral devices to support pharma companies' combination products sprint to market. For example, the on-body injector platform,



Nemera offers fully integrated services to market parenteral combination products.

Symbioze®, administers complex, large-volume drugs, such as monoclonal antibodies, with an adjustable flowrate. The sustainable device features a reusable electronic part and disposable module. "Technically, Symbioze is a complex device, yet it offers simplicity without overcomplicating user steps nor compromising patients' experience," says Cecile Gross, Global Category Manager Parenteral, Nemera. The main innovation lies in keeping the sterility between the two modules, ensuring patient's safety.

To avoid breakages, alternatives to glass prefilled syringes are on the market today, such as plastic-based syringe (COP). PFS manufacturers are also working on reducing silicon tungsten residues to prevent undesirable reactions between drug formulation and devices. "Our premium passive safety device add-on for prefilled syringes, Safe'n'Sound®, a passive safety device, highly customizable, available in 1mL and 2.25mL, is compatible with ISO glass syringes and 1mL COP PLAJEX™ syringe," says Ms. Gross.

She continues: "We offer continuous holistic support, including assembly equipment implementations to avoid breakage and other defects during manufacturing processes, optimizing the line's adaptation for our device to avoid recalls."

A Safe'n'Sound and Terumo PLAJEX 1mL-long prefillable syringe combination product has been launched in several markets for biosimilar administration to treat chronic inflammatory diseases. Ms. Gross says: "Thanks to our regulatory expertise, we helped our customer navigate the complex regulatory landscape to file specific combination product dossier registration in USA, Europe, and Japan."

Nemera also offers reusable and disposable pen injector platforms, including PenDura, PenOne, PenVario, and PenHV to treat diabetes, obesity, hormone imbalance, and osteoporosis among others, and are all ergonomic user friendly.

Novocol Pharma: Simplifying Lyo With a Cartridge-Based Reconstitution Solution

Novocol Pharma is a CDMO specializing in sterile cartridge fill-finish, supporting clinical-phase and commercial customers with turnkey services from product development to final device assembly. Through its device division, Duoject Medical Systems, Novocol offers drug delivery design services and solutions, including a portfolio of reconstitution, injection, and safety systems.

According to Eric Lee, Business Development Director, Novocol Pharma, the company is well-positioned in fill-finish of cartridge-based injectable products, a key format in autoinjector, pen injector, and wearables-based delivery platforms, and offers device assembly capabilities for cartridge-based pen injectors with equipment compatible with pen injector devices from leading global suppliers.

In addition, solutions from Duoject align with the growing trend of patient-centric drug delivery systems. "As the demand for self-administration continues to grow, there is an emphasis on safety features to reduce needlestick injuries," he says. Such solutions include the Falcon safety device, a prefilled syringe safety system, and PenPrep EVO, a cartridge-based reconstitution system, which both prevent needle exposure during patient use.

Novocol offers a complete solution to the challenges presented by drug reconsti-

tution, particularly the multi-step process with the PenPrep EVO device and in-house sterile cartridge filling services. This allows users to reconstitute a lyophilized drug product vial with a diluent cartridge. Once reconstituted, the mixture is drawn back into the cartridge for self-administration use with cartridge-based pen injectors.

Mr. Lee explains that a notable example of this turnkey offering includes a recent product lifecycle management project for a commercially marketed drug product in vial format that was only stable in lyophilized form. The application required patient self-administration several times a week using multiple vials, syringes, and needles. "By introducing the PenPrep EVO reconstitution device, a diluent cartridge that was developed and produced at Novocol, and a commercially available pen injector, the patient experience for the drug product was greatly enhanced, resulting in several improvements," he says. This includes replacing and simplifying multiple components and processing steps using one reconstitution device (containing both the drug vial and diluent cartridge), and pen injector device for self-administration. Another benefit is improved patient safety and eliminated risk of needlestick injury during the drug reconstitution process though PenPrep's needle safety feature.

Noxilizer: NO_2 Sterlization Maintains Drug Integrity

Noxilizer offers pharmaceutical, biotech, and medical device companies an ultra-low temperature sterilization process. Nitrogen dioxide (NO_2) sterilization is an alternative to ethylene oxide (EO) and hydrogen peroxide (VHP). NO_2 sterilization can operate between 10°C-30°C, offers minimum vacuum pressure, and performs surface sterilization with little to no residuals while maintaining drug integrity.

Maura O. Kahn, Senior Vice President, Commercial, Noxilizer, recounts how one global biotech company product team was evaluating multiple syringe types and sterilization methods, including EO and NO_2. Noxilizer staff became part of the product development team, conducting feasibility studies to assess the syringe brands and designs, vacuum budget, lethality cycles to confirm the most challenging location and initial cycle parameters, and ingress and external residuals. The biotech company identified a syringe design candidate that reduced risk to the product during the manufacturing process. Testing determined that only NO_2 sterilization worked with this syringe design. Since 2019, the company has executed a number of sterilization studies with their product and packaging. They have completed sterilization validation at two locations. This product will be submitted for regulatory approval in 2023 and commercial product is expected in 2024.

Ms. Kahn explains that, for pharmaceutical and biotech companies with large product portfolios in one therapeutic area, developing a standard delivery device and sterilization method will accelerate product development and time to market. As an example, she says that Noxilizer has worked with a global biotech company for more than four years as the company evaluated a number of syringe designs and sterilization methods, including EO, VHP, Peracetic Acid, and NO_2. She recalls that initial testing showed that only EO and NO_2 could achieve lethality in the most challenging location in the various syringe designs. Therefore, further testing was done to assess the pros and cons of both EO and NO_2. Extensive testing includes evaluating product and water-filled syringes that have been exposed to worst-case NO_2 cycle conditions – accelerated and real-time testing over 24 months. In both cases, product and water-filled syringes showed minimal to no NO_2 (or nitrates) ingress into the syringe contents. Drug integrity was maintained.

She says: "This, along with the other benefits of ultra-low sterilization, minimal vacuum, and short total process time when compared to EO, has led the company to select NO_2 sterilization for all products in development within this therapeutic area."

One World DMG: Injection Training Tools – The Key to Successful Onboarding

One World DMG designs and manufactures injection trainers and patient onboarding materials for the pharmaceutical and biopharmaceutical industries to ensure patient adherence and better health outcomes.

"The importance of helping patients as they begin their self-injection treatment is widely understood by the healthcare community," says Paul Randall, Vice President, One World DMG. "Successful training programs support the patient by educating, building confidence, and partnering with them throughout their health journey."

One World DMG works with patient educators and healthcare providers to gather insight into the needs of patients and their real-world experiences. Heidi Holden, Registered Dietician and Certified Diabetes Educator, shares her thoughts on the discrepancies in training experiences for patients: "I have different feelings about patient training in the office. There are sev-

eral factors involved. For example, how well was a nurse trained on that device? When was the last time they themselves trained on that device? How much time do they have to train the patient? Often, they really don't have the time to explain to the patient why they're taking the medication, what it does, so that's a problem."

"The transition from training in the HCP office exclusively to distributing trainers to patients has been adapted by One World DMG's long-term clients who see the benefits re-usable injection trainers provide in the home setting," says Jonathan Coe, Regional Director, One World DMG.

The benefits to the manufacturer are also evident in the example of a client who felt they had a design concern with their autoinjector that needed to be addressed. Using the One World's trainer for their autoinjector in human factors testing revealed a much less complicated issue that could be addressed by avoiding hefty and unnecessary expenses.

In addition to injection trainers, One World DMG's onboarding offerings include: patient starter kits, HCP injection demonstration kits, injection trainer packaging, instructions for use, quick reference guides, training videos and animations, as well as injection demonstration models – all designed to enrich the patient experience and overall safety.

"Manufacturers are putting more emphasis on safety in onboarding patients and training HCPs," says Diane Ranshous, Regional Director, One World DMG. "Injection trainers play a key role in improving patient safety. The ability to repeatedly practice the injection process with a safe "replication needle" familiarizes the patient with the product and the steps necessary to better ensure their protection. And while the technology will continue to develop, the need for strong training tools and educational support remains a critical component for both patients and HCPs."

Owen Mumford Pharmaceutical Services: PFS Delivers Doses >1mL

UniSafe® from Owen Mumford Pharmaceutical Services offers pharmaceutical companies the benefit of a spring-free safety device with a choice of 1mL and 2.25mL prefilled syringes. The absence of a spring provides ease of use and offers the patient an unobscured view of the syringe contents to check dose and clarity. In addition, there is no risk of pre-activation during transport and before use. UniSafe's design also features a secure integrated plunger that helps prevent removal and accidental drug spillage, and provides tamper evidence. The design also creates a device that has a simple final assembly.

"With the growing market in biologics and doses increasingly more than 1mL, UniSafe 2.25 provides a device for formulations with larger fill volumes," says Michael Earl, Director of Pharmaceutical Services at Owen Mumford. "UniSafe's design means that the operator can use the same technique as a typical syringe when administering medication."

In the US and Europe, regulations require needle-shielding devices to protect from needlestick injuries. Ideally, the needle protection should be integral to the device and require no additional user steps before and after use. UniSafe syringes feature a spring-free safety design with passive needle shielding that is employed as the user fully depresses the syringe plunger using the usual technique.

Mr. Earl shares that a key market driver influencing device design for parenteral administration is the need for more sustainable products. This includes raw materials (often plastic) as well as the manufacturing processes and transportation across the supply chain. Product packaging will also need to meet environmental standards, as changes in EU packaging regulations require all packaging to reach targets for recycling by specified dates.

"Designs that enable reduction, reuse or recycling are key methods to help achieve reduction in harmful emissions," he says.

Another trend is the addition of connectivity and data exchange to delivery devices, which help patients self-administer medication in their home setting and be less dependent on healthcare professionals (HCP). Data transferred from connected devices can confirm medication delivery, date, and time as well as help HCPs monitor patient compliance to their therapy and provide the necessary interventions to improve patient outcomes.

PCI Pharma Services: Needle Safety Will Be Commonplace In 5 Years

PCI is a global CDMO that provides integrated end-to-end drug development, manufacturing, and packaging solutions to increase product speed to market. "Our clients aim to accelerate their sterile drug development lifecycle and seek readily available capacity, reducing time to clinic and ultimately commercial launch," says Shawn Cain, Senior Vice President Development and Manufacturing, PCI. "PCI plays a key role in navigating development complexities and overcoming manufacturing and packaging challenges posed by both drug products and drug delivery devices."

PCI offers a full suite of sterile injectable drug development and manufacturing services, including formulation development, aseptic fill-finish of vials, bottles and prefilled syringes, and lyophilization, complete with dedicated in-house QC analytical and microbiological support. Complementing its core sterile manufacturing and filling solutions, PCI offers assembly, packaging, and labeling of advanced injectables such as prefilled syringes, syringes with needle safety devices, autoinjectors, and pens.

"Combining our expertise in sterile fill-finish manufacturing with specialist biologic packaging, labeling, and cold chain distribution provides a valuable end-to-end solution, simplifying the supply chain while delivering time and cost efficiencies," says Mr. Cain.

Just as fast tracking product to market is important so too is the fact that the pandemic fast tracked acceptance of self-injection, opening opportunities for new medicines and further improvements of drug delivery devices. "The growth in medical devices, be it needle safety devices for prefilled syringes or autoinjectors, pens and wearables platforms, has allowed the industry to take a significant step forward for standardization and for improving the patient experience," says Justin Schroeder, Global Vice President Technical Sales, PCI. "Likewise, these new pathways allow for administration of the growing number of biologic medicines that can be truly life-changing for patients."

Safety is at the core of self-administration. Both the economics and the manufacturing technologies have progressed to make needle safety a standard. "We continue to see that where sponsor companies develop advanced delivery forms such as an autoinjector, there is absolutely a consideration for a PFS-NSD (needle safety device) as an interim lifecycle solution or as a complementary option to the autoinjector platform to serve all markets and pathways for administration," explains Mr. Schroeder. "In addition, where clinical trials had traditionally been executed in vial format, and PFS platforms were more of a commercial stage drug delivery solution, we are now seeing more sponsor companies integrating PFS-NSD (and AI) into their clinical trials. This can provide multiple benefits, including more patient-friendly drug delivery, improved patient retention in trials, shortening duration of the trials, and more impactful study data. These factors are of significant benefit for filing and regulatory approval acceleration. I believe in less than 5 years it will be uncommon to find a PFS that does not offer some type of needle safety mechanism."

It is also quite common to select packaging materials during the drug development process to ensure product compatibility and to identify potential for product contamination that could affect product stability or efficacy. In parallel, physical testing of the PFS and assembled pen or autoinjector is critical.

PCI's European sterile fill-finish facility in Leon, Spain, entered into an agreement with a mid-sized biopharmaceutical company that was looking for a technology transfer of their oncology prefilled syringe product. Mr. Cain explains that the project began with the program in early development; it was a complex subcutaneous injection in suspension product with a challenging step of sieving during suspension compounding. The challenge was that this sieving step was to be performed under aseptic conditions, as the product suspension could not be terminally sterile filtered. At the point of project initiation, the client had only performed this process under non-aseptic conditions. PCI process engineers worked to scale up the batch and optimize the process of sieving by redesigning the formulation process. This was accomplished by modifying the equipment and processing components to execute the sieving process in both a GMP and aseptic manner. Initially, the sieving process did not work at the commercial scale, so PCI initiated a Design of Experiments (DoE) program to explore other alternatives to the sieving step without impacting the CQAs or CPPs of the drug product. "After multiple DoEs and stability studies, we successfully developed a more robust scalable process with positive stability results and sterility assurance," says Mr. Cain. "This project has now progressed to registration batches pending FDA regulatory review for US market supply."

Recipharm: Autoinjector Relies on Gas, Not Spring, for Gentle Delivery

Recipharm delivers design, development, manufacture, and sterile fill-finish of injectable drug products. This includes autoinjectors, blow-fill-seal, prefilled syringes and cartridges, vials, and ampoules. The company handles various formulations, including liquids, lyophilized, and dry powders.

Recipharm has a partnership with Sensyo Pharmatech for injectable manufacturing in Morocco and has a development center in Solna, Sweden, which develops formulations for multiple routes of administration. In addition, a device center in King's Lynn, UK, offers full flexibility to parenteral drug developers with the proprietary VapourSoft®-powered injection devices, capable of delivering high-viscosity formulations. VapourSoft is a

compact energy source using liquefied gas, rather than a spring. Through gentle release of a pressurized vapor, the device powers viscous drug delivery through a fine needle with minimal user effort. "This technology can enable the self-administration of formulations with viscosities of up to thousands of cP using relatively fine needles to improve patient comfort," says Louise Righton, Head of Strategic Marketing – Advanced Delivery Systems, Recipharm.

VapourSoft-powered devices can be tailored to the formulation viscosity, fill volume, size of needle, and drug delivery time, and are compatible with standard prefilled syringes. They also include an integrated needle safety system.

While self-administered devices traditionally take a long time to develop, Ms. Righton says the development of VapourSoft is a significant advancement. "These platforms provide ready-made device designs that require only minimal customization to meet the needs of the drug formulation and the Target Product Profile (TPP)," she says. "Thanks to this development, we can expect the cost and time required to develop new combination drug products, and to provide sterile fill-finish, to significantly reduce over the next few years, enabling more injectables to benefit from self-administration."

Considering quality when drafting the TPP for the product is also crucial to making the right choices in formulation and device development to minimize the risk of problems occurring at commercialization, she says. Including factors such as the final device and packaging can ensure that proper materials and design are selected to minimize the risk of breakage and to prevent leaching or ingress of oxygen, which can degrade the product and reduce shelf life. "By developing a product with the final storage conditions and packaging configuration in mind, it is possible to prevent breakage, leaching, and contamination from occurring in the first place," says Vincenza Pironti, PhD, Strategic Marketing Director, Recipharm. "Adopting a Quality-by-Design mindset can help achieve this goal, as it ensures a commitment to quality, and to addresses all potential quality risks embedded in the entire development process from the beginning of the project."

In 2020, Arcturus engaged Recipharm to support the manufacture of clinical trial supplies of Arcturus' COVID-19 vaccine candidate in an ongoing Phase I/II clinical trial. Further, the company needed to manufacture and release more than 100,000 units of ARCT-154 mRNA vaccine finished drug product in support of clinical Phase III trial study.

When Arcturus presented its mRNA vaccine candidate to Recipharm, it was at the stage of a frozen product, a ready-to-administer sterile injectable for Phase I and II clinical trials. The inherent cryogenic logistics and storage costs associated with mRNA vaccines, as well as their intended markets (under-served populations with less access to developed healthcare infrastructures), created an additional burden for Phase III clinical trial and commercialization.

"To mitigate these challenges, Recipharm collaborated with Arcturus on the technology transfer, qualification, and cGMP manufacturing of the lyophilized product to ease the complexities of distribution and extension of vaccine shelf life," explains Dr. Pironti. "Timelines were successfully accelerated to meet the demands of the global COVID-19 pandemic response."

Sanner Group: Functionality & Design Are Equally Important

Innovation and growth in biologics have created innovation and growth in PFS, including RTU/RTF formats and polymer PFS. Sanner GMbH produces polymer prefilled syringes and accessories, as well as custom device solutions. "Polymer PFS are becoming a more viable alternative to glass syringes," says Viola Wedl, Product Management Medtech, Sanner Group. "COC material, for example, offers a solution to breakage, and advancements in coatings are closing the performance gap compared to glass."

Sanner carefully considers patients' needs with regards to design and user-friendliness at the earliest stage of development. Patient and user safety is equally important. A common safety feature consists of a mechanism that withdraws the needle after injection and locks it in a safety cap. But, there are other PFS features that contribute to overall device safety, such as enlarged finger grip accessories produced in two-component injection molding. There are also special plunger rods that enable the user to rotate the rod within the syringe chamber to allow a smooth injection of all substances, regardless of viscosity.

"We developed a new concept of syringe accessories for a customer in aesthetic medicine," she explains. "This included ergonomic and modern plunger rods, and finger rest extensions to form the prefilled syringe to a complete system. As functionality and design are equally important, we shaped finger rest enlargements with a non-slip grip leads to ensure greater safety and ease of use of the PFS. We also manufactured piston rods and finger rest enlargements using two-component injection molding in the smallest shot weights for improved grip and safety dur-

ing injection. The ability to rotate the syringe barrel in the finger rest enlargement allows the syringe needle to be optimally aligned, so the syringe does not have to be applied several times."

Stevanato Group: Coating Technology Reduces Product/Packaging Interactions

Stevanato Group combines products, technologies, and services to create tailored solutions for pharma clients. The latest addition to the company's syringe portfolio is the Nexa Flex™ pre-sterilized polymer syringe, available in both cyclic olefin polymer (COP) and cyclic olefin copolymer (COC) materials – complementing the Nexa® platform's existing glass container solutions.

"Nexa Flex has an optimized silicone-oil distribution along the barrel that improves gliding performance while minimizing particles – while its 100% camera inspection guarantees consistent cosmetic quality," says Silvia Gallina, Product Manager for the syringe platform at Stevanato Group. "Moreover, it uses a tungsten-free polymer molding process to guarantee compatibly with even the most sensitive drugs."

To address the complex needs of new biologic drugs, Stevanato Group's portfolio includes the Alba® prefillable syringe platform. "This solution features a cross-linked coating technology, based on standard silicone, that significantly reduces the interaction between the drug product and the container surface – a crucial development for ophthalmic drugs and highly concentrated formulations prone to silicone aggression," says Ms. Gallina.

Another development is the growth in at-home treatment driving a renewed focus on usability and a switch from intravenous to subcutaneous drug delivery to improve the patient experience. "User-friendly and automatic delivery systems, such as autoinjectors, are becoming increasingly important to increase treatment adherence and improve the patient experience, enabling a successful transition from hospital to at-home treatment," says Enrico Barichello, Product Manager for the syringe platform at Stevanato Group. "The rapid growth of autoinjector use requires drug products to be stable in liquid form, a staked-in needle syringe for example, can accommodate a maximum dosage volume of 2mL-2.2mL, and it is becoming more important that drug containers are well fitting and do not react with the medication to avoid functionality and delivery challenges." For this reason, Stevanato Group introduced ready-to-use vials, cartridges, and syringes that respond to the life cycle management strategies of the industry.

Technology is key to ensuring large volumes of prefilled syringes can be distributed with consistently high-quality standards. To that end, Stevanato Group implemented technology solutions into its glass processes to ensure reliable inspection and detection of dimensional and cosmetic defects, as well as particle contamination, with 100% in-line control or in-process controls.

"Combining technology innovations on both process and product enables delivery of a high value-added system that provides superior performances in terms of mechanical resistance, functionality (smooth break loose and gliding forces, i.e. inferior to 5 N), and container geometries suitable for device integration in all the critical contact parts," says Mr. Barichello. "Additionally, a robust manufacturing process and improved controls help reduce the risk of rejection of containers, thus decreasing costly re-inspection of products."

To further enhance the quality of its products, Stevanato Group is currently undergoing an evaluation to implement Artificial Intelligence in the glass primary packaging manufacturing processes.

Beyond the manufacturing facility, primary container traceability is critical for improving production efficiency and quality. "Glass container traceability marks each primary container with a unique identity," explains Mr. Barichello. "This machine-readable 2D barcode code allows each container to be tracked at every manufacturing process, from forming through to filing and automated inspection. This delivers significant process and quality benefits for both the glass container producer and pharma companies."

Terumo Medical Care Solutions: PFS Offers Silicone Oil-Free Container

As part of Terumo Medical Care Solutions, the Pharmaceutical Solutions Division manufactures, supplies, and supports projects associated with its polymer-based prefillable syringes, as well as injection needles, infusion sets, and novel drug delivery devices.

One example would be an ophthalmic drug being developed in a prefilled syringe application with a customer. "There are increasing numbers of patients who require ophthalmic drug administration by intravitreal injection, triggered by the rapidly aging global population," explains Philippe Lauwers, Technology Development Director, Terumo. "And there are still unmet challenges to designing a prefilled syringe that can safely administer

ophthalmic drugs via intravitreal injection."

For example, he says that silicone oil is deposited in the eye's vitreous body after repeated injections and cannot be evacuated. It is also a challenge to precisely deliver a dose as low as 50 microliters, which is a typical administration volume for currently available ophthalmic drugs.

In addition to understanding the challenges of ophthalmic drug delivery so too is the importance of understanding and evaluating the potential adverse impact of primary container components on the stability of drug products. In particular, complexly-engineered biotech drug products have shown to be more prone to stability concerns when exposed to silicone oil, tungsten oxides, glue residues or high energy sterilization processes.

To address these issues, Terumo's polymer prefillable syringes offer a full silicone oil-free container closure and eliminate the use of tungsten pins and adhesives during the production process. And, by applying steam sterilization, Terumo avoids the generation of free radicals typically associated with high energy sterilization processes which may potentially impact the stability of the sensitive drug product inside the prefilled syringe.

"We are helping our customers solve these challenges with solutions such as our proprietary silicone oil-free technology, as well as precision molded polymer prefillable syringes," says Mr. Lauwers.

Ypsomed AG: Family of Injectors for Longer Durations, Larger Volumes

Ypsomed AG has developed a new autoinjector platform for liquid medications with volumes ranging from 1.5mL to 5.5mL, the latter of which is the latest addition to the company's YpsoMate family of devices, and is based on established YpsoMate 2.25 Pro technology. YpsoMate 5.5 enables the self-administration of larger volume medications for treating cancer, as well as rare and autoimmune diseases.

YpsoMate 5.5 features two-step handling already proven in other YpsoMate models: Remove the cap and push on the skin. The injection process is triggered automatically. YpsoMate 5.5 is equipped with a handgrip for comfortable handling and stability during injection. A continuous visual and audible signal gives the user good control over the entire injection process.

"During product design, special focus was placed on providing optimal support for larger volumes and a longer injection duration," explains Ian Thompson, Vice President, Account & Business Development, Ypsomed AG.

YpsoMate 5.5 also features an integrated, prefilled syringe developed in collaboration with SCHOTT. "It leverages existing standards and components to optimize processes for pharmaceutical customers and shorten time-to-market, reduce development risks, ensure suitability for sensitive drugs, and facilitate compatibility with existing filling equipment," he says. "The result of the joint development with SCHOTT is the syriQ BioPure 5.5mL, a large-volume, prefillable syringe with integrated needle."

Ypsomed and SCHOTT have collaborated to provide new standards for both large-volume 5.5mL staked needle syringes and 1mL ready-to-use (RTU) cartridges for the YpsoMate 5.5mL autoinjector and YpsoDose 10mL patch injector, respectively. "The 10mL YpsoDose has undergone thorough internal testing and comparative studies with pharma customers," says Mr. Thompson. "Ypsomed is committed to the successful industrialization and commercialization of YpsoDose as a new state-of-the-art patch injector."

YpsoDose will be supplied to initial customers for clinical trials later this year. "For pharma companies to consider and invest in patch injectors, they need to access reliable device technology and implement standard filling and final assembly processes that provide a solution that fulfils the needs of patients and healthcare providers," he says. "Fulfilling these requirements with well-thought-out device technology will allow the patch injector market to grow significantly and become established as the third self-injection device class, complementing the maturing and expanding markets for pen injectors and autoinjectors."

Reference

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BIOGRAPHY

Cindy H. Dubin is an award-winning journalist who has been reporting on the pharmaceutical industry for more than 20 years about formulation development, drug delivery, and drug quality.

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Ascendia Pharmaceuticals: Innovative Solutions to Challenging Problems

Jim Huang, PhD
CEO & Founder
Ascendia Pharma

Ascendia Pharmaceuticals is a specialty Contract Development and Manufacturing Organization (CDMO), dedicated to the invention and development of pharmaceutical drug products though its proprietary enabling formulation technology platforms: LipidSol®, NanoSol®, EmulSol®, and AmorSol®. The company provides formulation, analytical, and manufacturing services to pharma and biotech companies, working collaboratively to provide innovative solutions to challenging drug delivery problems and to create advanced medicines across all modalities.

Drug Development & Delivery recently interviewed Jim Huang, PhD, CEO and Founder of Ascendia Pharmaceuticals, to discuss how his company expanded its people, capabilities, and facilities to meet and exceed customer expectations from early to late-state development and how this investment allows Ascendia to continue be an expert in sophisticated formulations, as well as cGMP sterile and non-sterile clinical trial and commercial manufacturing.

Q: Can you tell us what makes Ascendia unique and different from other CDMOs?

A: Unlike many other CDMOs that offer capacity, Ascendia is a CDMO that truly provides "solutions" through its proprietary nanotechnology platforms, state-of-art R&D, and cGMP sterile and nonsterile manufacturing capabilities. Our enabling formulation technologies often make possible for many new drug delivery projects, which seems impossible for other CDMOs and drug developers.

Ascendia's expertise involves finding the most effective method of drug delivery for challenging therapeutic modalities, such as poor water-soluble and low bioavailable small molecule entities, peptides, biologics, and RNAs. Ascendia was started with the goals to use its enabling platform technologies to address solubilization and bioavailability challenges and to expedite the development of drugs faster to clinic and market. With our internal know-how and expertise in analytical and formulation technologies supported by the PhD scientists and state-of-the-art facilities and equipment,

Ascendia is poised to take the challenges of insoluble molecules and biologics delivery from R&D to cGMP manufacturing within 6-9 months.

Our comprehensive range of capabilities enables clients to optimize their drug product formulation prior to initiating expensive clinical development. We provide practical, seamless, customized formulation solutions that enable rapid advancement of modalities from discovery to clinical testing. We provide trial formulations suitable for initial animal studies and toxicology studies using our nano-emulsion, amorphous solid dispersions, lipid nanoparticles, controlled-release or long-acting injectables, and nano-particle engineering approaches. We conduct pre-formulation testing, formulation approach comparisons, dosage form design, and formulation optimization. By working with Ascendia, our clients can quickly determine the feasibility of multiple technical approaches in parallel, thus improving the probability of formulation success and reducing the time required to make critical early stage formulation decisions.

Q: Can you review Ascendia's platform technologies and why are they so important?

A: Ascendia's technology platforms include NanoSol (nanoparticle engineering), EmulSol (nanoemulsion), AmorSol (amorphous nanoparticles) and LipidSol (lipid nanoparticles). These formulation technologies are designed to customarily apply to all therapeutic modalities with different types of properties, thus offering our customers "one-stop-shop" drug delivery service that increases the chance of success and reduces time to proof of concept (PoC) for their drug candidates.

Ascendia's platform technologies are developed around important issues associated with the delivery of therapeutic modalities inside animal and human bodies: drug solubility, permeability, stability, and ultimately drug bioavailability and PK/PD profiles. From the delivery perspective for small molecule entities, as more and more new molecules come out of discovery that are practically insoluble and very poorly bioavailable, our enabling solubilization technologies often make possible many difficult new drug delivery projects. Using our technologies, bioavailability of molecules can be improved significantly, opening the bottleneck for further animal tox studies for INDs, early phase human clinical development, and eventually PoC for new drug candidates.

Whereas from the drug delivery perspective of large molecules, such as peptides, biologics, and RNAs, many of them have problems associated with instability, short systemic half-life, and poor membrane permeation into the target cells. Our technologies are capable of encapsulating those therapeutic candidates into nanoparticles or matrices that potentially enhance stability, enable longer duration of drug release, and increase drug permeation into the target cells.

Q: Can you expand on the newly developed LipidSol® technology platform?

A: LipidSol is Ascendia's newly developed platform technology in the area of lipid nanoparticles (LNPs) based on the lipid assemblies of varied structures and compositions. Those aggregates exist in lipid nanoparticles akin to the approved COVID LNP vaccine by Pfizer/BioNTech/Moderna, liposomes, stealth liposomes, solid lipid nanoparticles, nanostructured lipid carriers, immunogenic liposomes, and cubosomes, among others. Our LipidSol technology is primarily aimed at addressing the delivery issues of biologics, RNA, peptides, and small molecules by enhancing their efficacy and safe administration through injectable (IV, IM, SubQ) and inhalation for the treatment of life-threatening ailments and life cycle management. For the best design and encapsulation efficacy of modalities, the LNP lipid structures, size, charge, and morphology play a key role in protecting and carrying the payload to target sites via systemic circulation. The longer the circulation means that the lipid nanoparticles are stable and are prevented from being captured by Kupffer's cells in blood streams, and therefore, provide a better mechanism for controlled delivery of modalities through an extended period. In addition, to better deliver the payload into the target cell, cationic lipids sourced from commercially available GRAS material or from a proprietary lipid library are accessible to Ascendia for use in LNP formulations.

Ascendia has its state-of-art research, scale up, and cGMP sterile manufacturing capabilities for lipid nanoparticles that other CDMOs do not offer. In conjunction to our lipid analytical method development, aseptic processing and fill & finish, and ISO 5/7 clean room facilities, we have equipment ready to use for different LNP processes, namely solvent injection, film rehydration, nano-assembly, microfluidization, tangential flow filtration (TFF), and lyophilization, from small lab scale to large production scale. Our main equipment for LNPs includes a microfluidic chip mixer, NanoAssemblr, high shear microfluidizer, high pressure homogenizer, extruder, and rotavapor, among others, which offers clients a top down and bottom up approach to formulation techniques.

Q: How relevant are LNPs to liposomes?

A: Liposomes are truly a first generation of lipid nanoparticles. Designed with phospholipids and similar class of lipids, traditional liposomes form bilayer structures with interior lipophilic and hydrophilic interstitial spaces. Because of its unique structure, liposome can entrap drug modalities that are amphiphilic in nature, not only the hydrophobic drugs if they are solvated in the bilayers, but also the hydrophilic drugs if they are entrapped inside the aqueous interstitial space. Immunogenic and stealth liposomes are another class of liposomes derived from modified headgroups with the goal to target specific diseased tissues or to circulate longer without being taken up by reticular epithelial systems (RES). Liposomes designed as Lipoplexes with special complexing abilities with polynucleotides with ionizable lipids may provide another route for administration of vaccines, RNA, and biologics.

Q: Can LipidSol® be used for peptides, biologics, and RNA delivery?

A: LipidSol technology encompasses lipid nanoparticles to address a variety of therapeutic modalities, including biologics, RNA, peptides, and small molecules that can't be delivered to the diseased tissues by traditional formulation approaches. LipidSol enables encapsulation of drugs in the LNPs by utilization of fatty acids and polar headgroup entities that are commercially available and listed in FDA inactive ingredient database (FDA IID) or that is accessible to a novel lipid library. In addition to traditional liposomes, other LNPs, such as immunogenic and stealth liposomes, solid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and cubosomes, will play an important role as more challenging modalities are discovered. Ascendia's footprint in LNP technology through LipidSol will continue to address the challenges in formulations requiring controlled delivery of small molecules, peptides, biologics, plasmids DNA, and RNAs.

Q: Can LipidSol® be applied to poorly soluble molecules?

A: LipidSol can be designed with unique attributes capable of encapsulating poorly soluble molecules. Given the flexibilities in their design with interior fatty acid composition and headgroup exterior, LipidSol is an excellent vehicle to carry the payload of insoluble molecules and deliver them to affected sites by avoiding the toxicity and improving the bioavailability of drugs. Prepared by solvent evaporation, solvent injection, or film re-hydration methods, poorly water-soluble drugs could be complexed with lipid as amorphous form, entrapped in the biolayer, or precipitated as a nanoform inside the interior phase of the LNP. The particle size of LipidSol can be controlled to unimodal distribution by repetitive extrusion or high pressure/shear process and sterile filtration through 0.22-micron filters. If required, LipidSol can be lyophilized for improving shelf-life as a ready-to-use formulation by reconstitution in diluents like 0.9% saline, D5W, or buffers prior to injection.

Q: Can LipidSol be used in dosage forms other than injectables?

A: LNPs, especially those with liposomal characteristics, are ideally suited for injectables (IV, IM, and SubQ) because of their delicate structures and well-defined unimodal particle size distribution. Whereas LNPs in general, particularly solid lipid micro/nanoparticles, and nanostructured lipid particles designed with different a class of lipids, can be used in oral, inhalation, nasal, ocular, and topical formulations depending on the composition of lipids, and their compatibility for the designated route of administration. It has been reported in literature that lipids could promote drug absorption due to their affinity to topical mucosal layers or due to enhanced lymphatic absorption or tight junction opening in the GI tract. Selection of excipients for LipidSol from the FDA's IID database may provide a guideline for their suitability in the intended route of administration.

Q: What is the future trend of LNPs as drug delivery systems?

A: Fueled by new and innovative therapeutic modalities and needs for CDMOs with the right expertise in formulation development and aseptic manufacturing, we foresee that in the area of biologics, RNA, vaccine peptides, and ADCs will continue to dominate the LNP applications with leaps and bounds, and we at Ascendia are ready to take this opportunity to grow further. As more oncology, immunology, anti-inflammatory, and viral diseases continue to lead the forefront of innovative medicines, more pharma and biotech companies will look for outsourcing either due to lack of expertise within, or lack of manufacturing capabilities at the premises. Ascendia is well positioned to take the lead working with those in need for our services in LNP drug development and manufacturing. ◆

VACCINE TECHNOLOGY

Solving the Challenges & Introducing New Strategies for Influenza & COVID-19 Protection

By: Paul Radspinner, MBA and Pamuk Bilsel, PhD

INTRODUCTION

Currently available influenza vaccines have three key problems to overcome to improve their modest efficacy: their limited ability to block influenza infection and prevent the virus from spreading, short durability of immune responses, and the inability to address drifted or "mismatched" strains of flu. While vaccine developers have worked to address these problems by exploring new approaches to the design, manufacture, and/or administration of influenza vaccines, no single approach has yielded an approved vaccine that addresses all three problems.

FluGen aims to change that with its M2SR (M2 Deleted Single Replication) influenza vaccine technology, which overcomes many of the limitations of today's influenza vaccines. M2SR is based on a live but replication-deficient influenza virus delivered as an intranasal spray, resulting in broader and more durable immune responses, especially at the site of infection, and greater efficacy at preventing infection and illness.

FluGen also believes its M2SR technology can help address the shortcomings of approved COVID-19 vaccines, which are now facing some of the same challenges as influenza vaccines. FluGen is developing the M2SR technology as a vector platform for respiratory infectious diseases that includes an influenza/COVID-19 vaccine. This vaccine, either alone or in combination with other influenza and/or COVID-19 vaccines, could provide broader and more durable protection against infection by influenza and SARS-CoV-2 viruses.

The following describes where the key challenges arise for current influenza vaccines, how FluGen's technology addresses them, and why FluGen believes combination vaccines will be key to providing ultimate protection against both influenza and COVID-19.

WHERE & WHY CURRENT INFLUENZA VACCINES FALL SHORT

Influenza vaccines fall into three broad categories: inactivated influenza vaccines (IIVs), which deliver inactivated virus by intramuscular injection; recombinant influenza vaccines (RIVs), which deliver recombinant hemagglutinin (HA) antigen, also by intramuscular injection; and live attenuated influenza vaccines (LAIVs), which contain a live but weakened virus, delivered as an intranasal spray.

The largest and perhaps most notable problem with IIVs and RIVs is their modest efficacy, which is 50%-60% at best, and well below the NIH's target of 75%. Three factors can contribute to this limited efficacy: the vaccines' ability to stimulate antibodies primarily against just one viral antigen, influenza A HA; the stimulation of mainly serum antibodies; and viral drift or "mismatch" between the vaccine and the circulating viruses.

The type of immune protection provided by IIVs and RIVs is a function of their manufacturing processes. For IIVs, the virus is grown in eggs, then inactivated to produce a vaccine that primarily presents HA, a surface protein the virus requires for cell entry, to the immune system. For RIVs, recombinant baculoviruses expressing HA from the viral strain of interest are grown in insect cells, and the HA is purified for use in the vaccine. Because they are delivered via injection, IIVs and RIVs elicit high titers of

hemagglutinin-inhibiting (HAI) antibodies in serum. But they do not elicit serum antibodies to other important viral antigens, such as neuraminidase (NA) or nucleoprotein (NP).

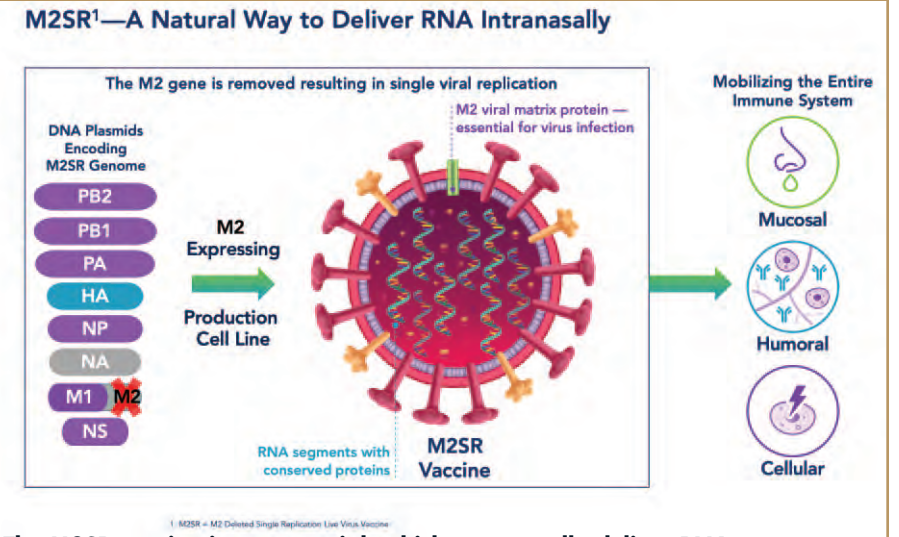
Moreover, systemic HAI antibodies provide no local immunity at the site of infection, which is the nose and upper respiratory tract. This means IIVs and RIVs cannot prevent infection by the virus; they can only prevent or minimize illness arising from the infection. Intranasal LAIVs may stimulate local immunity; but because the vaccine relies on virus replication to generate protective immunity, the efficacies of these vaccines are limited in individuals who have pre-existing influenza immunity that prevents vaccine virus replication.

Viral drift is another factor that adversely affects the efficacy of all three categories of vaccines. Viral drift is the tendency for the influenza virus to accumulate changes in the HA and NA surface antigens over time. When this happens, the antibodies elicited against one strain of influenza virus eventually will not recognize and neutralize newer, "drifted" versions of the virus.

Similarly, viral drift can result in mismatches between the selection of the viral strain(s) used to manufacture the annual vaccine – which is based on predictions by the Centers for Disease Control and Prevention (CDC) and other health authorities about the strains likely to circulate during the Northern Hemisphere's flu season – and the strains that actually circulate during flu season. When the mismatch is high, vaccine efficacy can be quite low, as was the case during the 2014-2015 flu season, when overall efficacy of the vaccine was less than 20%.

Additionally, current vaccines provide only a few months of protection, which is shorter than the actual flu season; and because they do not protect against infection – only illness – people can still contract the virus, shed it, and transmit it to others, even if they never experience any overt symptoms of infection.

FIGURE 1



The M2SR vaccine is an essential vehicle to naturally deliver RNA intranasally. By removing the M2 gene, single viral replication is ensured while mobilizing all major immune system components.

M2SR: MOBILIZING THE ENTIRE IMMUNE SYSTEM WHERE IT COUNTS

FluGen's M2SR vaccine technology addresses all of the aforementioned issues with influenza vaccines. M2SR is a live influenza virus in which M2, a protein the virus requires for replication, has been genetically deleted. The M2 protein is added back during manufacturing, allowing for production of the single replication virus. Because it is a live and intact virus, M2SR stimulates immunological responses to HA as well as NA, NP, M1, and other conserved viral antigens. But because it cannot replicate more than once in the vaccinated individual, M2SR does not lead to any viral shedding or sequelae that are associated with LAIVs based on replication-competent viruses.

While FluGen has developed all four components needed for a quadrivalent M2SR influenza vaccine, our initial clinical testing has focused on the H3N2 component, which we call H3N2 M2SR. This is because the H3N2 subtype of influenza A causes the most serious illness, especially in older adults, and current vaccines typically have the lowest efficacy against this subtype.

M2SR is delivered as an intranasal spray, which stimulates durable, local immunity at the site of infection in the form of mucosal antibodies, serum antibodies, and cellular (T cell) immunity.[1,2] M2SR also elicits cross-reactive serum antibodies that were shown to last at least 6 months in clinical testing.[1] M2SR to date has demonstrated an excellent safety and tolerability profile, even with a dosing window 10- to 100-fold higher than for other intranasal vaccines, because M2SR replicates only once.

Additionally, through its combination of viral antigens and intranasal delivery, M2SR elicits cross-reactive responses: that is, it remains efficacious even when the in-

fecting strain of the virus does not exactly match the strain used to make the vaccine.

For example, last year, we published results from a Phase 2 challenge study, demonstrating that an H3N2 M2SR vaccine based on a 2007 strain protected vaccinated subjects against subsequent challenge with a highly drifted H3N2 strain from 2015.[3] This ability of M2SR to circumvent the problem of viral drift is arguably its single greatest advantage over current vaccines.

We have just completed dosing and monitoring subjects in a Phase 1b trial, funded by the US Department of Defense, of H3N2 M2SR to test the hypothesis that combining our vaccine with an approved influenza vaccine will offer the best of both worlds to older adults: the local, durable immunity of M2SR; and the high titers of serum HAI antibodies elicited by injected vaccines that are essential to protecting older adult patients. To that end, the trial is evaluating the safety and immunogenicity of H3N2 M2SR alone, Fluzone High Dose inactivated influenza vaccine alone, and the combination of both vaccines, in a total of 305 adults aged 65-85. The last subject was enrolled in September, and to date, no severe adverse events have been reported.

We expect to have the immunogenicity data from the trial in the first quarter of 2023, and we hope those data will demonstrate a true breakthrough in achieving vaccine efficacy in this highly vulnerable population.

ADDRESSING THE PROBLEMS EMERGING FOR COVID-19 VACCINES

The mRNA vaccines against COVID-19 were developed with astonishing speed during the pandemic and have saved millions of lives worldwide since their approval. Their importance in combatting the pandemic is clear and cannot be overstated.

However, it is becoming equally clear that COVID-19 vaccines have many of the same weaknesses as marketed influenza vaccines. These include serum antibody immunity lasting only a few months; lack of immunity at the site of infection; lack of robust protection against drifted strains, most recently the Omicron variant of SARS-CoV-2; and lack of protection against infection, leading to viral shedding and transmission by vaccinated individuals who contract the virus.

The introduction of the bivalent COVID-19 booster, which includes the viral spike protein from the original strain of SARS-CoV-2 and its Omicron variant, is designed to provide broader protection than the original mRNA vaccines. Yet only about 13% of the US population has received the booster; and meanwhile, more than 3,000 people are hospitalized with COVID and more than 3,000 die from it every week.[4] It seems we must either settle for COVID-19 becoming like influenza – endemic and not always well controlled by vaccines – or change our vaccine strategy.

One shift in strategy is already underway: recognizing the importance of local and mucosal immunity in blocking a respiratory virus, researchers have been investigating intranasal vaccines for COVID-19. A second strategy is combining influenza and COVID-19 vaccines, which would offer a single solution to both viruses, especially given that COVID-19 appears to be falling into a seasonal pattern similar to influenza.

FluGen is pursuing both strategies with an intranasal, combination vaccine for influenza and COVID-19. However, our approach differs from other combination vaccines in development, which either combine the components of individual influenza and COVID-19 vaccines or deliver mRNA from both viruses. Our approach inserts the receptor binding domain (RBD) of the SARS-CoV-2 spike protein into the DNA plasmids encoding the M2SR genome. In this way, we use M2SR as a vector to deliver a SARS-CoV-2 antigen, creating a bivalent COVID/Influenza M2SR vaccine that provides immune protection against both viruses.

In mice, we have shown an M2SR-vectored, COVID/Influenza vaccine, based on the H3N2 virus and encoding the RBD from the original SARS-CoV-2 Wuhan strain, elicited robust production of neutralizing antibodies against both Wuhan and the Delta variant, while maintaining identical titers of HAI antibodies and local immune responses to influenza as our M2SR H3N2 vaccine alone. Moreover, the M2SR-vectored vaccine not only generated mucosal IgA and IgG antibodies against Wuhan, but also against variant Omicron strains, without impeding the influenza responses. We are currently analyzing data from a study in hamsters challenged with SARS-CoV-2.

Initially, our bivalent vaccine could be used alone or as an add-on to existing influenza and/or COVID-19 vaccines, to provide the local mucosal, humoral, and cellular immunities that those vaccines do not. We are currently continuing preclinical studies of our M2SR-vectored COVID/Influenza vaccine, and plan to take the H3N2 version forward into clinical testing, as we have already gathered a great deal of clinical safety and toxicity data for the H3N2 M2SR influenza vaccine itself.

ENVISIONING A DIFFERENT FUTURE FOR INFLUENZA & COVID PROTECTION

Longer term, we envision developing a quadrivalent M2SR-vectored COVID/Influenza vaccine, in which each of the four M2SR components of the influenza vaccine could deliver an RBD from a different SARS-CoV-2 variant and/or different conserved epitopes from the viral spike protein that also elicit antibodies. Here, too, our M2SR technology has distinct advantages.

Live quadrivalent vaccines can be difficult to develop for two reasons: the potential for one viral strain in the vaccine to out-replicate the others; and the potential for one strain to be immunodominant, suppressing the immunity elicited by the other strains. Both results can compromise the ability of a live quadrivalent vaccine to provide the full range of intended immune responses.

FluGen does not expect an M2SR-vectored, quadrivalent COVID/Influenza vaccine to have these issues. Our vaccine replicates only once, so one strain cannot out-compete the others; and we have shown that each component of the vaccine generates immune responses without interfering with the responses generated by the other components. As with our influenza vaccine, a quadrivalent COVID/Influenza M2SR vaccine could be combined with other COVID-flu vaccines to generate the ultimate protection against both viruses.

With this combination vaccination strategy, the biopharma industry could truly solve the efficacy, durability, and drift problems of current influenza and COVID-19 vaccines. The strategy could also reduce or eliminate the need to predict which influenza strains will circulate during flu season, or to play "vaccine catch-up" as new SARS-CoV-2 variants of concern emerge.

Ultimately, we and FluGen envision a world in which the deadly, endemic, and pandemic influenza and SARS-CoV-2 viruses are more effectively managed, where consumers have more confidence that their vaccinations will prevent disease, and where morbidity and mortality will be greatly reduced. ◆

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BIOGRAPHIES

Paul Radspinner is Co-founder, President, and Chief Executive Officer of FluGen Inc. As President & CEO, FluGen has raised over $40 million in capital and completed multiple human clinical trials with M2SR. After completing his MBA at Northwestern University's Kellogg Graduate School of Management, he spent over 15 years in management roles overseeing international pharmaceutical operations, marketing, and business development with Eli Lilly and Company. After his time at Lilly, he managed the pharmaceuticals portfolio, including Vitamin D analogs at the Wisconsin Alumni Research Foundation (WARF) for the University of Wisconsin-Madison. He entered the Madison biotech scene when he took on the role of Vice President of Business Development for Deltanoid Pharmaceuticals, Inc. and then started FluGen. In 2008, he was elected to the Board of Directors for BioForward, the Wisconsin state biotechnology organization, where he served as President. He is a member of the Boards of Directors for Plumb Pharmaceuticals and Co-D Therapeutics.

Dr. Pamuk Bilsel is Chief Scientific Officer at FluGen Inc., bringing nearly 15 years of corporate biotechnology and management experience in vaccine research against infectious diseases. Prior to joining FluGen, she was involved in developing DNA vaccines based on cell-mediated immunity against influenza and malaria at Pharmexa-Epimmune, where she served as Director of Molecular Biology. At Pentamer Pharmaceuticals, a San Diego start-up venture, she worked on subunit vaccines against respiratory syncitial virus using virus-like particle technology. Preceding that, she worked at Aviron generating live attenuated influenza vaccine strains in addition to studies with the cold-adapted influenza vaccine which was eventually launched as MedImmune's FluMist. She earned her PhD in Cell and Molecular Biology from the University of Nevada, Reno, and completed her post-doctoral training at St. Jude Children's Research Hospital with Dr. Kawaoka.

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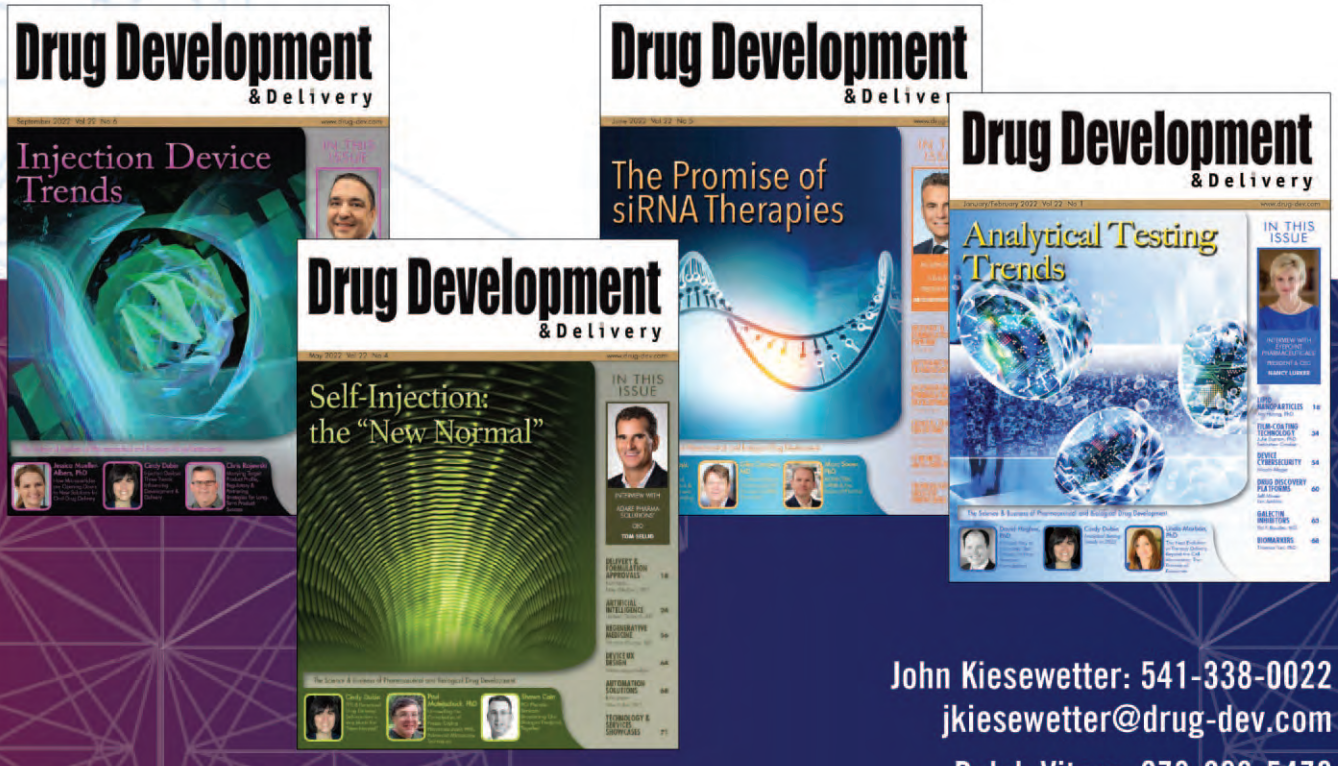

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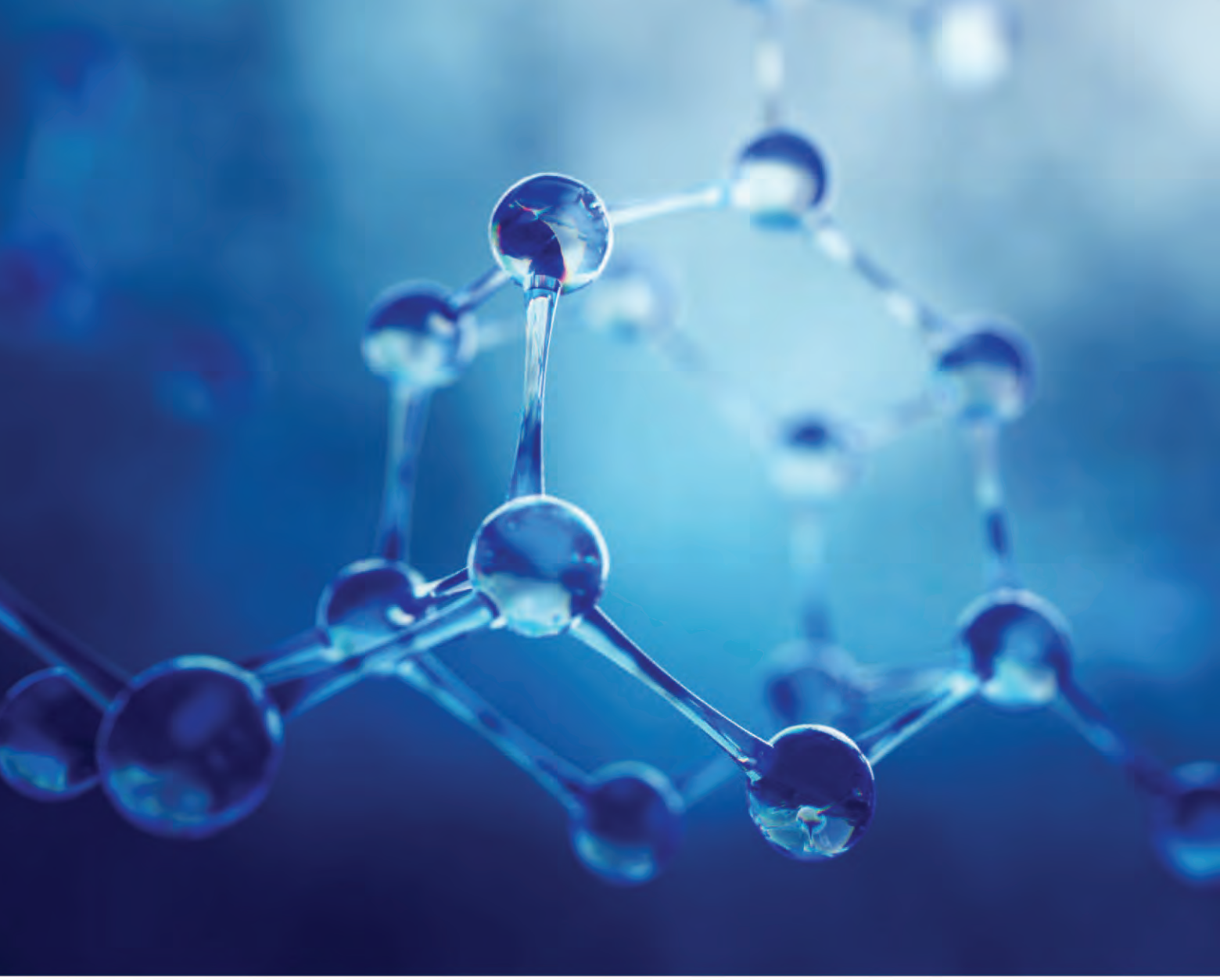

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