Drug Development & Delivery

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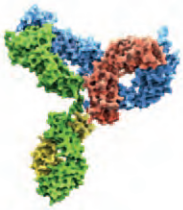
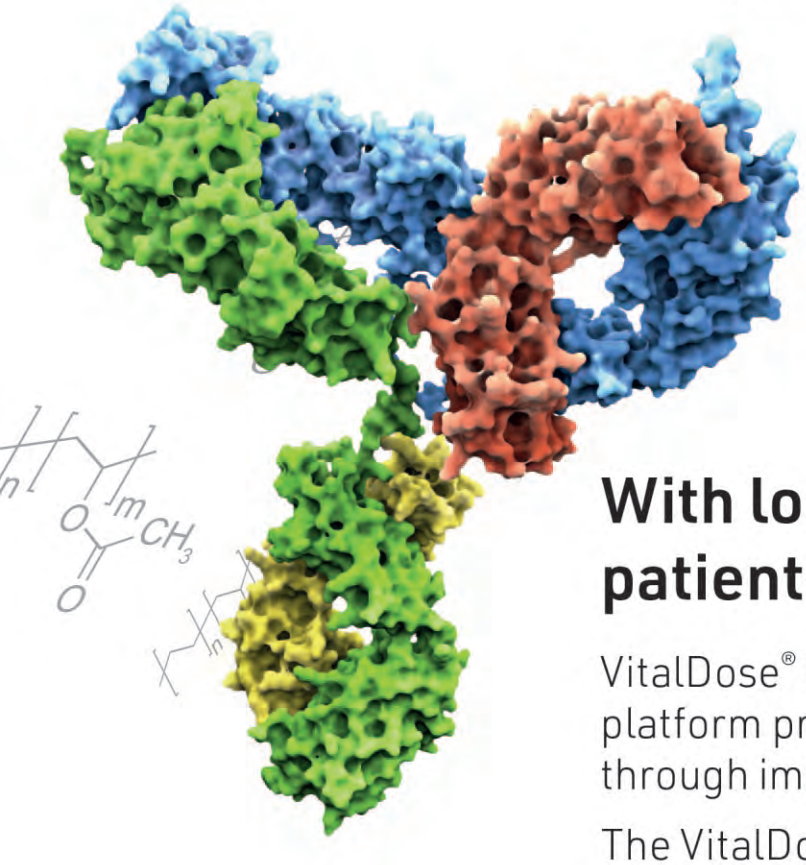
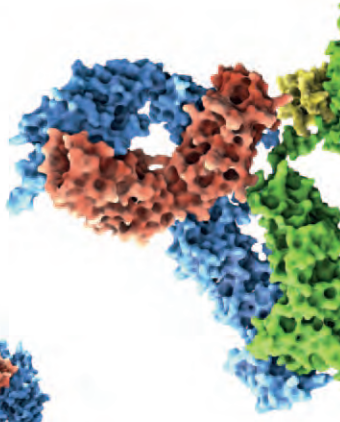
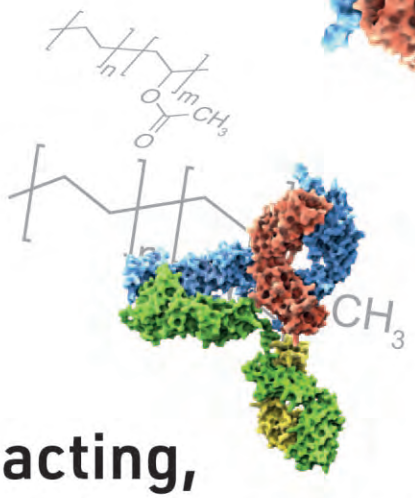


Sustained Drug Delivery







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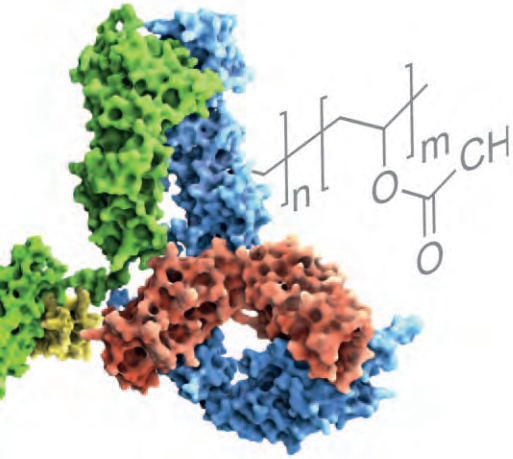

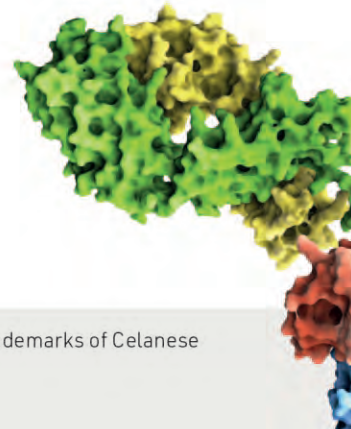

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Outsourcing Development & Manufacturing

"The rising need for novel drugs to battle infectious and chronic diseases is one of the main drivers of the global formulation development and manufacture outsourcing market. Valued at $22.5 billion in 2021, the market is expected to skyrocket to more than $51 billion by 2031. Higher R&D expenses, a desire to shorten time spent on these activities, and the fact that many companies lack the resources to perform these functions will only strengthen the contract sector."

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INTEGRATED CDMO SERVICES. ADARE DOES IT. FIND OUT HOW.

Adare Pharma Solutions is a global technology-driven CDMO providing end-to-end integrated services, from product development through commercial manufacturing and packaging, with small molecule expertise focusing on oral dosage forms. Adare's specialized technology platforms provide taste masking, controlled release, solubility enhancement, and patient-centric dosing solutions. With a proven history in drug delivery, Adare has developed and manufactures more than 65 products sold by customers worldwide.

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Evonik Launches Next-Generation Peptide for Biopharma Applications

Evonik now offers cQrex® KC, a performance-boosting peptide for cell culture media used in the manufacture of biological drugs. The new peptide enables cell culture process developers and media formulators in the biopharmaceutical industry to optimize cystine supply and increase cell culture productivity.

cQrex KC is the latest addition to Evonik's toolbox of cQrex cell culture ingredients designed to increase efficiency and productivity in cell culture processes used to produce monoclonal antibodies, vaccines, viral vectors, and cell therapies. The market for biological drugs – greater than €250 billion in 2022 – continues to grow, with several thousand products in the pipeline.

"We are excited about the opportunities cQrex KC offers to our customers. By enabling increased flexibility in media formulation and bioprocess design, we are helping more efficient production of biopharmaceuticals," said Martin Schilling, Director of Cell Culture Ingredients at Evonik's Health Care business.

Adding cQrex KC to Evonik's market-leading cQrex portfolio and accompanying application services, strengthens the company's offerings of System Solutions. Nutrition & Care, the life sciences division at Evonik that is home to the Evonik Health Care business, aims to increase its share of System Solutions from 20% today to more than 50% by 2030. System Solutions are defined as multicomponent systems tailored to a specific customer need.

L-cystine is a key amino acid in cell culture. Sufficient supply is critical to support cell growth and production of biopharmaceuticals. However, L-cystine is hardly soluble in cell culture media at neutral pH, so it is difficult to supply enough of this amino acid to cells cultured in modern industrial processes that rely on chemically defined media.

cQrex KC is a highly pure and soluble peptide designed to address the challenge of L-cystine supply in cell culture. It allows the formulation of concentrated and pH-neutral feed and perfusion media, as well as basal media, therefore intensifying and simplifying complex production processes. By increasing the cell proliferation, viability and cell-specific productivity, cQrex KC also contributes to higher antibody titers and increased overall productivity of biological drugs.

Evonik Health Care is a leader in cellular nutrition and a global development and manufacturing partner to the world's leading pharma and biopharma companies. By leveraging six decades of industry leadership, Evonik Health Care provides the market with robust pharmaceutical-grade cell culture ingredients and solutions including amino acids, cQrex peptides, lipids, and other performance boosters.

OLON Enters ADC Market

OLON Group recently announced the start of construction of a new facility at its Rodano site (Milan, Italy) which will be entirely dedicated to managing and producing Ultra-Potent compounds, used for example as payloads and payload-linkers for antibody-drug conjugates (ADCs), one of the most promising emerging cancer therapies, which combines the effective killing power of small molecule cytotoxins and the highly specific targeting ability of monoclonal antibodies (mAbs).

"Actually, about 80% of the ADCs either approved or under development contains this type of payload, such as Dolastatins or Maytansnoids," said Giorgio Bertolini, Senior VP R&D Olon Group. "And there are also other highly strategic classes of cytotoxic payloads, such as Anthracyclines, Camptothecin, and Calicheamicin."

The Italian group, with years of expertise in HPAPIs, has invested €22 million in a new facility dedicated to these ultra-potent compounds. The ultra-high-containment production line will produce high-potency and toxic products and will therefore reach containment level OEB6 (target OEL 10 ng/m3).

The new project foresees the complete construction of a new building, within which a second "shell" will be built, containing the production facility and the quality control and research and development areas, as well as all auxiliary facilities. This complete, closed-loop system will include all steps of the process: synthesis, isolation, drying, and analysis: an ultra-high-containment plant.

The first phase of the construction, to build the payload research and development area, has already begun and completion is foreseen by H1, 2024. Once completed, the company will move on to the second stage of finalizing the production line by creating the QC and GMP Production areas, with the installation of industrial production equipment.

For the Italian-based contract development and manufacturing organization (CDMO) which has worked with highly potent APIs (HPAPIs) – including anti-cancer drugs and cytotoxic – for over half a century, the decline of the blockbuster, high-volume model in oncology and the rise of niche therapies based on precision medicine are creating new opportunities for continued growth.

Olon is one of few suppliers in the global API market able to integrate every level of containment from the initial API development to commercial manufacturing and from a few grams to hundreds of kilograms.

Olon Group is a global leader in the development and production of active pharmaceutical ingredients (APIs) for CDMO and generic markets, integrating chemical synthesis and biological processes while always embracing the highest international safety, quality, and environmental standards.

With one of the longest track records of the API industry, having deep development expertise and a broad set of advanced technologies, we are the partner of choice which enables our client's molecules to enter the market successfully.

Olon has a global network of 11 manufacturing sites and 7 R&D centers across the globe. Thanks to our 2,300 employees, including 300 highly experienced and qualified R&D experts, we represent a highly innovative and reliable partner.

Oxford BioTherapeutics & Boehringer Ingelheim Agree on 2-Year Extension to their Second Multi-Year Collaboration in Cancer Immunology

Oxford BioTherapeutics Ltd. (OBT) recently announced it has extended its second multi-year collaboration with Boehringer Ingelheim for an additional 2 years. With this extension, further programs will be added into the existing collaboration, with the goal to enable the development of novel cancer immunotherapies in areas of high unmet patient need.

The two partnerships between OBT and Boehringer Ingelheim were initiated in April 2013 and October 2020. They are both focused on the discovery of novel tumor targets enabled by OBT's proprietary OGAP discovery platform for Boehringer Ingelheim's unique immuno-oncology and ADC platforms, contributing to the company's aspiration of transforming the lives of people living with cancer with the ultimate goal of curing a range of cancers.

Christian Rohlff, PhD, Chief Executive Officer of Oxford BioTherapeutics, said "Last month marked the 10-year anniversary of our partnership with Boehringer Ingelheim and it is fitting to mark this anniversary by extending our collaboration both in time and in value. Over the past decade, we have built a successful relationship with Boehringer Ingelheim's cancer research, now in its third phase, through high-quality outputs enabled by our proprietary OGAP discovery platform. Since 2013, the company has selected three targets discovered using OGAP, of which two programs have led to therapeutic assets in Phase 1 clinical development. We look forward to the next phase of our highly successful partnership and to continuing to work together to develop innovative first-in-class treatments for patients with difficult to treat cancers."

A major differentiator between OBT's discovery platform and other approaches is the retention of the link between individual patient samples through to the design of therapeutic antibodies and diagnostic patient selection tools, which increases the overall success rate of these novel compounds transitioning into clinical development.

Under the terms of the extended agreement, Boehringer Ingelheim is responsible for the development and commercialization of treatment candidates that interact with the novel targets identified by OGAP. OBT will receive research funding as well as success-based development and regulatory milestone payments and royalties on potential future product sales.

Oxford BioTherapeutics (OBT) is a clinical-stage oncology company based in Oxford (UK) and San Jose (US); with a pipeline of first-in-class immuno-oncology (IO) and antibody-drug conjugate (ADC) based therapies designed to fulfil major unmet patient needs in cancer therapeutics. These include bispecific, Chimeric Antigen Receptor T Cell (CAR-T), Antibody Drug Conjugate (ADC) and Antibody Dependent Cell-mediated Cytotoxicity (ADCC) therapeutics.

OBT's first clinical program, OBT076, initiated expansion in a US Clinical Trial in 2021 in patients with advanced or refractory solid tumors, including gastric, bladder, ovarian and lung cancer, where CD205 is overexpressed. Infiltration of tumors by immunosuppressive cells correlates with adverse outcomes (lower progression free and overall survival), suggesting that this process contributes to the progression of several cancers.

Viridian Therapeutics Announces Partnership With Drug Delivery Innovator Enable Injections

Viridian Therapeutics, Inc. recently announced a new partnership with Enable Injections, a company developing and manufacturing the enFuse innovative wearable drug delivery system for volumes of up to 25 mL.

"As we expand our pipeline beyond TED and assess the unmet needs of patients living with other serious and rare diseases, it's clear that convenient drug delivery is an important issue," said Scott Myers, President and CEO of Viridian. "We believe Enable's proprietary technology can contribute meaningfully to our goal of delivering therapeutic advances while reducing patient treatment burden as well."

"Enable Injections is excited to partner with Viridian to utilize the enFuse technology to enhance the patient experience," said Michael D. Hooven, Enable Injections' Chairman and CEO. "The enFuse on-body delivery system was engineered with the patient in mind—the hidden needle and hands-free delivery allows patients to have increased flexibility, improved convenience, and the ability to administer medication discreetly, whether at home via self-administration or in the clinic."

This partnership, which applies exclusively to areas outside of Viridian's established TED portfolio, underscores the company's commitment to patient-centric innovation.

Viridian Therapeutics is a biopharmaceutical company focused on engineering and developing potential best-in-class medicines for patients with serious and rare diseases. Viridian's expertise in antibody discovery and engineering enables it to develop differentiated therapeutic candidates for previously validated drug targets in commercially established disease areas.

Viridian is advancing multiple candidates in the clinic for the treatment of patients with thyroid eye disease (TED). The Company has initiated its first global Phase 3 trial called THRIVE to evaluate the safety and efficacy of VRDN-001 in patients with active TED. Viridian is also evaluating VRDN-001 in a Phase 2 proof-of-concept trial in patients with chronic TED. In addition to its program for intravenously administered VRDN-001, the company is advancing three candidates for its subcutaneous strategy with the goal of providing a more conveniently administered therapy to patients with TED. Viridian is also developing multiple preclinical assets in autoimmune and rare diseases. Viridian is based in Waltham, MA. For more information, visit www.viridiantherapeutics.com.

Cincinnati-based Enable Injections is a global healthcare innovation company developing and manufacturing drug delivery systems designed to improve the patient experience. Enable's body-worn enFuse delivers high-volume pharmaceutical and biologic therapeutics via subcutaneous administration, with the aim of improving convenience, supporting superior outcomes, and advancing healthcare system economics. The investigational enFuse system has not been approved for use by any regulatory agency and is currently not approved for commercial use. For more information, visit www.enableinjections.com.

Valo Therapeutics Announces First Patient Dosed With PeptiCRAd-1 – Innovative Immuno-Oncology

Valo Therapeutics Oy (ValoTx) recently announced the first patient has been treated in its Phase 1 trial of PeptiCRAd-1 (Peptide-coated Conditionally Replicating Adenovirus) in three tumor types.

PeptiCRAd-1 is an innovative approach never before used combining two clinically proven cancer immunotherapy approaches: oncolytic adenoviruses and tumor-specific peptides for the generation of strong systemic cytotoxic T-cell responses against multiple tumor antigens. This is achieved by coating the company's proprietary oncolytic adenovirus with immunogenic tumor-specific peptides thereby directing the immune system to specifically target and kill cancer cells. No other oncolytic virus therapy delivers tumor targets in this simple but effective and adaptable way.

The first patient has been administered with PeptiCRAd-1 successfully, without any initial safety concerns and the Safety Data Committee has concluded that the study can continue enrolment. Following this green light, further patients are now being recruited at the Krankenhaus Nordwest in Frankfurt, and at the National Center for Tumor diseases (NCT) in Heidelberg.

PeptiCRAd-1 combines the power of a tumor-specific adenovirus (expressing immune-stimulatory molecules CD40L and OX40L) with immunogenic tumor peptides derived from NY-ESO-1 and MAGE-A3 proteins thereby generating tumor-specific, cytotoxic T-cells that will attack and kill cancer cells.

The trial is designed to evaluate the safety, immune activity, and tumor response of PeptiCRAd-1 alone and then in combination with the immune checkpoint inhibitor (CPI), pembrolizumab in 15 patients with either melanoma, triple-negative breast cancer or non-small cell lung cancer. The trial will explore local and systemic immune activation, and immune responses against the tumor-specific NY-ESO-1 and MAGE-A3 peptides, as well as clinical responses. It includes intensive immuno-monitoring of tumor and blood samples from patients to confirm the mechanism of action of PeptiCRAd-1 and to identify biomarker-related outcomes, among other signals of clinical benefit.

The Coordinating Investigator for the trial, Prof. Dr med. Elke Jäger, from the hospital Krankenhaus Nordwest in Frankfurt am Main's Department of Oncology and Hematology, one of Germany's top oncology treatment centers with a wealth of immuno-oncology experience, added "We are very excited to be involved in this study. This is a truly innovative immuno-therapy approach which has shown great promise in the pre-clinical setting. We hope to be able to translate this to positive clinical outcomes for patients."

Valo Therapeutics Oy (Helsinki) is an immunotherapy company developing antigen-coated oncolytic viruses as therapeutic vaccines against cancer. The ValoTx lead platform, PeptiCRAd (Peptide-coated Conditionally Replicating Adenovirus), was developed out of the laboratory of Professor Vincenzo Cerullo at the University of Helsinki. It turns oncolytic adenoviruses into powerful activators of systemic anti-tumor cytotoxic T-cell immunity without the need to generate and manufacture multiple genetically modified viruses. PeptiCRAd-1 is the company's lead product made up of its virus VALO-D102 coated with MAGE-A3 and NY-ESO-1 peptides. The company is also developing other neoantigen strategies.

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Roquette Announces Strategic Investment & Innovation Agreement With Beren Therapeutics P.B.C.

Roquette recently announce a strategic investment with Beren Therapeutics P.B.C., and the launch of an innovation agreement to expand the full potential of Beren's cyclodextrin technologies and their medicinal applications.

Beren is a vertically integrated biopharmaceutical company focused on addressing the world's most significant health challenges. Roquette recognizes the revolutionary potential of Beren's research to transform the market and the lives of millions of patients worldwide.

"Our refusal to stand still has helped us establish a leading market position and identify where the next big development in the pharma space is likely to emerge – and that's what we see in our new relationship with Beren Therapeutics," said Paul Smaltz, Vice President of Pharmaceutical Solutions at Roquette. "We've been impressed by Beren's work as a Public Benefit Corporation and their innovations in manufacturing and drug development. Beren's research indicates incredible untapped horizons in the cyclodextrin market that enable tackling the world's greatest health challenges. This relationship can open up expanded capabilities for us in chemistry, manufacturing, controls (CMC) management, advancing safety protocols and regulatory registration."

"Teaming up with Roquette is another step forward in our efforts to work across our ecosystem to accelerate 'access for all,'" said Frank Langston, Beren's Senior Vice President of Business Strategy. "We're showcasing how outside-the-box collaboration can lead to greater societal impact and allow us to rapidly explore the untapped potential of our technology beyond our core business."

"Working with Roquette is a natural fit. Bringing our teams closer together can only lead to faster innovation and opportunities that wouldn't exist if we weren't looking to engage outside our traditional domains," added Jason Camm, CEO of Beren Therapeutics, P.B.C. "Both our missions align around pushing the boundaries of scientific innovation to benefit humanity, particularly when it comes to efficient and sustainable manufacturing processes."

Roquette is a family-owned global leader in plant-based ingredients, a pioneer of plant proteins and a leading provider of pharmaceutical excipients. Founded in 1933, the company currently operates in more than 100 countries, has a turnover of about 5 billion euros, and employs more than 8,000 people worldwide. Life and nature have been our sources of inspiration for decades. All our raw materials are of natural origin. From them, we enable a whole new plant protein cuisine; we offer pharmaceutical solutions that play a key role in medical treatments; and we develop innovative ingredients for food, nutrition, and health markets. We truly unlock the potential of nature to improve and save lives. Thanks to a constant drive for innovation and a long-term vision, we are committed to improving the well-being of people all over the world. We put sustainable development at the heart of our concerns, while taking care of resources and territories. We are determined to create a better and healthier future for all generations.

Cell & Gene Therapy CDMO Targets North American Growth With Major US Acquisition

uBriGene is expanding into the US market with the acquisition of a state-of-the-art GMP manufacturing facility from NASDAQ-listed company Mustang Bio, Inc. The cell & gene therapy (CGT) CDMO has an established global footprint with two GMP manufacturing facilities in China and its headquarters in Vancouver, Canada. The latest move will see uBriGene expand its global headcount to over 500 employees.

The newly acquired manufacturing site in Worcester, Boston, MA, has a suite of clinical facilities for the production of cell and gene therapies, as well as providing contract analytical services.

The 27,000-sq-ft site is designed for multiproduct cGMP manufacturing of multiple gene-modified cell types and has fully integrated technology transfer, quality control testing, manufacturing development, warehousing, and cGMP storage capabilities. The site has successfully manufactured two different CAR-T products to support clinical trials and has performed extensive analytical and process development work to support the products.

"This acquisition is important to uBriGene's commitment to support the development, clinical, and commercial supply of cell and gene therapies to meet rapidly growing demand," said Alex Chen, President of uBriGene. "We hope to work together with the University of Massachusetts Medical School to continue to grow the advanced therapy manufacturing ecosystem in the Worcester region.

This partnership enables us to expand rapidly to create a North American presence and offer the same high-quality cell and gene therapy development and manufacturing capabilities for the US that we currently provide in Asia, including to support Mustang Bio's lead clinical-stage CAR-T program."

The newly acquired facilities have been developed to a very high-quality standard with a cGMP-compliant quality system.

"Mustang is excited to be partnering with uBriGene to advance our novel leading cell therapy programs and leverage their global manufacturing and development expertise to progress our advanced cellular therapies through clinical trials in the US," said Manny Litchman, Mustang Bio's Chief Executive Officer.

As part of the purchase, uBriGene will take over the clinical manufacturing of Mustang Bio's MB-106, a CAR-T cell therapy treatment for a wide range of hematologic malignancies, including Waldenstrom macroglobulinemia, a rare malignant disorder of the bone marrow and lymphatic tissues, which could improve the lives of patients if successful.

The move is set to generate significant high-value job creation and growth opportunities in the greater Boston area. uBriGene is looking to expand its team at the site further by hiring more than 50 new technical specialists over the next 12 months. The facility is located in close proximity to the University of Massachusetts Chan Medical School and other renowned technical universities which will enable uBriGene to draw on the world-class skills and talent available on the doorstep.

Upperton Pharma Solutions Increases Oral Dosage Form Capabilities at Its Nottingham HQ

Upperton Pharma Solutions has expanded its oral dosage form capabilities at its newly built headquarters in Nottingham, UK. Part of Upperton's £15m investment program announced in January this year, the state-of-the-art facility has benefited from a significant investment in large, commercial-scale equipment offering powder blending up to 250 kg per batch, capsule filling up to 40,000 capsules/hour, dry granulation processing up to 100kg/hour, and tablet pressing up to 120,000 tablets/hour.

The expanded capabilities will enable Upperton to continue to meet the growing demand for its oral, nasal, and pulmonary dosage form development and GMP manufacturing services, as well as increase its ability to support larger scale, later stage development.

The new equipment is currently being installed and commissioned in a dedicated 700-sq-ft cleanroom, which is one of 10 GMP suites housed in Upperton's 50,000-sq-ft facility expected to be fully operational by the end of 2023.

Upperton CEO Nikki Whitfield said "This investment is a pivotal next step as we move towards the completion of our new facility. It will enable us to extend our support for our clients' manufacturing needs from early development phases through to Phase 3 clinical trials, registration batches and subsequent commercial manufacture, all at one, single site."

Upperton's new £15m, 50,000-sq-ft. facility in Nottingham has been designed to handle highly potent molecules and controlled drugs, and will allow a significant increase in research and development laboratory space alongside a 10-fold increase in GMP manufacturing space.

"We are delighted with the progress we have made. The investment allows us to increase our current development and manufacturing capacity as well as expand our solid dose and spray drying offerings to address the growing needs of our customers," added Whitfield. "We will also be able to support existing and new clients further in their product development journey, ensuring a consistent and streamlined pathway to approval from product development through to late stage and commercial."

Upperton uses its expertise to develop a wide range of non-sterile, finished dosage formats for its clients. Alongside dosage form development, the company also specializes in spray drying, a particle engineering technology that can be used to ensure targeted delivery of drugs to the lungs and nasal cavity, or to provide solutions to pharma clients who have challenges with poorly soluble molecules. For more information, visit https://upperton.com.

MetrioPharm Receives Orphan Drug Designation for the Treatment of Duchenne Muscular Dystrophy

MetrioPharm AG recently announced the US FDA has granted Orphan Drug Designation for MP1032 for the treatment of Duchenne muscular dystrophy. DMD is the most common form of muscular dystrophy. It is a genetic disorder characterized by progressive muscle degeneration; symptom onset is in early childhood, usually between the ages of two and three. The disease primarily affects boys causing severe muscle loss and heart failure, while girls can show milder symptoms as well. DMD shortens life expectancy significantly. Existing standard therapies consist of treatment with high dose corticosteroids for decades that lead to serious side-effects and can only slow disease progression.

"Currently, DMD cannot be cured, but it can be treated," said MetrioPharm CSO and Co-founder Dr. Wolfgang Brysch. "These treatments have serious side effects that heavily impact patients' quality of life. With MP1032 we aim to improve the tolerability of treatment while also further slowing down disease progression. Our goal is to improve both safety and efficacy in the long-term treatment of DMD patients."

"The orphan drug designation is granted by the FDA for drug candidates that the FDA considers a promising new treatment. In a designated orphan development, timelines are shorter, and costs are lower compared to indications with larger patient populations," added MetrioPharm CEO Thomas Christély. "The Orphan Drug Designation for MP1032 in DMD by the FDA is a very important achievement; it takes us one crucial step closer to obtaining an accelerated market approval of our lead compound for Duchenne patients. MetrioPharm plans to initiate a Phase II clinical trial in DMD in 2024."

DMD is classified as an orphan disease of high unmet medical need. FDA orphan drug designation is granted to investigational therapies addressing rare medical diseases (affecting fewer than 200,000 people in the US). Orphan drug status provides benefits to drug developers, including assistance in the development process, exemptions from FDA fees and 7 years of post-approval marketing exclusivity.

MetrioPharm has conducted preclinical studies in cooperation with the patient organization Duchenne UK. In these in vivo experiments, MP1032 was tested in an mdx model for DMD and compared to the effect of corticosteroids. MP1032 was able to enhance muscle strength, like the corticosteroid Prednisolone, but without the serious side effects of the latter. In a second preclinical study, executed by Eurofins, several biomarkers show that the combination of MP1032 with a 90% reduced dose of Prednisolone increases the efficacy to more than two and a half times the normal dose of Prednisolone. This supra-additive (synergistic) effect means that both substances, MP1032 plus Prednisolone, are more effective in combination than either substance alone.

LIXTE Biotechnology's Lead Clinical Compound Increases Effectiveness of Cancer Immunotherapy

LIXTE Biotechnology Holdings, Inc. recently announced a recently published article in the journal Cancer Research showed that PP2A, the pharmacologic target of LIXTE's lead clinical compound, LB-100, when inactivated in preclinical models of glioma, activates a complex intracellular signaling system, the cGAS-STING pathway. This leads to an activation of interferon signaling, an increase in MHC class I expression on tumor cells, an increase in CD8+ killer T cell proliferation, while at the same time reducing immunosuppressive tumor associated macrophages. Consequently, as shown in the article, PP2A inactivation sensitized the immunologically "cold" glioblastoma cells to immune checkpoint blockade therapy in vivo.

The May 23, 2023 article in the journal Cancer Research, titled PP2Ac Deficiency Enhances Tumor Immunogenicity by Activating STING-Type I Interferon Signaling in Glioblastoma, by Mondal et al. from the Department of Neurological Surgery, University of California, San Francisco.

John S. Kovach, MD, CEO and Founder of LIXTE, said "The case for combining LB-100 with immunotherapy is ever more compelling. We reported last year on emerging clinical evidence that PP2A inhibition may sensitize clear cell ovarian cancer patients to checkpoint inhibitors (https://ir.lixte.com/news-events/press-releases/detail/77/inactivating-mutations-in-scaffold-component-of-pp2a-the). We currently have one active multicenter trial in which LB-100 is combined with immunotherapy and chemotherapy in small cell lung cancer (NCT04560972), and are finalizing additional trials of LB-100 with immunotherapy for treatment of immunologically unresponsive tumors. Lixte has long been interested in determining whether LB-100 potentiates standard treatment of glioblastomas. Thanks to the work of Mondal et al., we are now keenly interested in assessing whether LB-100 facilitates immunotherapy of primary brain tumors, among other immunologically 'cold' tumors for which more effective treatments are needed."

Rene Bernards, Professor of Molecular Carcinogenesis at the Netherlands Cancer Institute and member of the LIXTE Board of Directors, added "Our own recent research provides yet another reason to combine LB-100 with immunotherapy as phospho-proteomic analysis of LB-100 treated colon cancer cells identifies mRNA processing as a major pathway perturbed by LB-100. As a consequence of LB-100 exposure, colon cancer cells contain a significant amount of incorrectly spliced mRNAs, which is a known source of neo-antigens that can help turn an immunologically 'cold' tumors 'hot' and vulnerable to immunotherapy."

LIXTE Biotechnology Holdings, Inc. is a clinical-stage pharmaceutical company focused on new targets for cancer drug development and on developing and commercializing cancer therapies. LIXTE has achieved a breakthrough demonstrating that its first-in-class lead clinical PP2A inhibitor, LB-100, is well-tolerated in cancer patients at doses associated with anti-cancer activity. Based on extensive published preclinical data (see www.lixte.com), LB-100 has the potential to significantly improve outcomes for patients undergoing various chemotherapies or immunotherapies. LIXTE's new approach has no known competitors and is covered by a comprehensive patent portfolio. Initial proof-of-concept clinical trials are in progress.

Catalent Adds New Cryogenic Capabilities at Shiga, Japan, Facility to Support Clinical Supply Demand for Cell & Gene Therapy Development

Catalent recently announced it has expanded the services and capabilities at its facility in Shiga, Japan, to include the storage, kitting, and distribution of advanced therapies at ultra-low temperatures for clinical trials.

State-of-the-art cryogenic freezers alongside material transfer equipment have been installed that are designed to retain the integrity of investigational advanced therapy products by minimizing their time-out-of-environment. The expansion forms part of Catalent's ongoing global strategy to increase its ability to handle, store and manage advanced therapies for clinical supply, and follows investments at its facilities in Philadelphia, Singapore, and Shanghai, China, in specialized, ultra-low temperature storage capabilities.

The 6,000-sq-m Shiga site opened in October 2021 to support customers both locally and globally, providing flexible clinical supply solutions, including primary packaging, Catalent's FastChain demand-led supply, white glove handling and logistics.

"The market in Japan for advanced therapies and new modalities continues to grow, along with the demand for companies such as Catalent that have the advanced infrastructure to handle the supply and distribution of these highly sensitive products, as well as the specialized expertise and comprehensive knowledge to manage these supply chains," commented Tadahiro Matsumura, Catalent's President of Japan. "This investment allows us to provide the optimum logistical solution for every customer's individual needs, and the foundation to increase capacity as requirements change and grow."

With sites in the US, UK, Germany, Singapore, Japan, and China, and an extended network of over 50 depots, Catalent's clinical supply services meet a broad range of international compliance and distribution requirements to support global clinical trials. For more information on Catalent's clinical supply services, visit https://www.clinical.catalent.com.

Catalent is the global leader in enabling pharma, biotech, and consumer health partners to optimize product development, launch, and full life-cycle supply for patients around the world. With broad and deep scale and expertise in development sciences, delivery technologies, and multi-modality manufacturing, Catalent is a preferred industry partner for personalized medicines, consumer health brand extensions, and blockbuster drugs.

Catalent helps accelerate over 1,000 partner programs and launch over 150 new products every year. Its flexible manufacturing platforms at over 50 global sites supply around 80 billion doses of nearly 8,000 products annually. Catalent's expert workforce of approximately 18,000 includes more than 3,000 scientists and technicians. Headquartered in Somerset, NJ, the company generated nearly $5 billion in revenue in its 2022 fiscal year. For more information, visit www.catalent.com.

Apellis Reports Top-Line Results from Phase 2 MERIDIAN Study in ALS

Apellis Pharmaceuticals, Inc. recently announced the Phase 2 MERIDIAN study investigating systemic pegcetacoplan for the treatment of amyotrophic lateral sclerosis (ALS) did not meet its primary endpoint of the Combined Assessment of Function and Survival (CAFS) rank score at Week 52. The study also did not meet key secondary efficacy endpoints. Systemic pegcetacoplan was well tolerated in the study, and the data were consistent with the established safety profile.

Based on the lack of efficacy, Apellis and Sobi plan to discontinue development of systemic pegcetacoplan for ALS. In April, Apellis and Sobi discontinued treatment in the open-label portion of the study, following a recommendation from an independent data monitoring committee.

"We are disappointed in the outcome of the MERIDIAN study, especially on behalf of the ALS community who has been waiting for new treatments for this complex and unrelenting disease. We would like to sincerely thank the study participants and their caregivers from around the world who contributed to this important research," said Jeffrey Eisele, PhD, Chief Development Officer, Apellis. "Our hope is that the data generated from this study will continue to support future research and development in ALS."

The full MERIDIAN dataset is being analyzed, and detailed data is expected to be presented at a future medical meeting.

The Phase 2 MERIDIAN study (NCT04579666) is a randomized, double-blind, placebo-controlled, multicenter study designed to evaluate the efficacy and safety of systemic pegcetacoplan in approximately 250 adults with sporadic amyotrophic lateral sclerosis (ALS). Study participants were randomized in a 2:1 ratio to receive pegcetacoplan or placebo while continuing to receive their existing standard of care treatment for ALS for 52 weeks. The primary endpoint of the study is the Combined Assessment of Function and Survival (CAFS) rank scores. Key secondary endpoints include measures of overall function, survival, lung function, and muscle strength. After 52 weeks, all study participants were to receive pegcetacoplan. To reduce the burden on people living with ALS and their caregivers, the study has been designed to minimize the number of in-clinic visits.

Pegcetacoplan is a targeted C3 therapy designed to regulate excessive activation of the complement cascade, a part of the body's immune system, which can lead to the onset and progression of many serious diseases. Pegcetacoplan is under investigation for several rare diseases across hematology, nephrology, and neurology. Pegcetacoplan is approved for the treatment of paroxysmal nocturnal hemoglobinuria (PNH) as EMPAVELI in the US, Australia, Canada, and Saudi Arabia and in the European Union and the United Kingdom as Aspaveli.

Apellis and Sobi have global co-development rights for systemic pegcetacoplan. Sobi has exclusive ex-US commercialization rights for systemic pegcetacoplan, and Apellis has exclusive US commercialization rights for systemic pegcetacoplan and worldwide commercial rights for ophthalmological pegcetacoplan, including for geographic atrophy.

Revvity Announces New License Agreement for Next-Generation Base Editing Technology

Revvity, Inc. recently announced a new license agreement with AstraZeneca for the technology underlying its Pin-point base editing system, a next-generation modular gene editing platform with a strong safety profile.

Dr. Alan Fletcher, Senior Vice President, Life Sciences at Revvity, said "Our fundamental goal for the Pin-point platform is to translate the technology from pre-clinical research into the clinic, and ultimately, impact patient lives. In that vein, we are delighted to announce this non-exclusive agreement with AstraZeneca to support their creation of cell therapies for the treatment of cancer and immune-mediated diseases."

The Pin-point system and the underlying base editing technology is designed to enable highly efficient and precise single and multiplex (multi-gene) editing without unintended impact on cell viability or functionality. Compared to traditional CRISPR technologies, which create double-stranded breaks in the DNA, this newer editing system uses a modified Cas enzyme that only nicks one strand of the DNA. This allows for a more controlled approach to gene disruption and base correction.

The Pin-point system differs from other base editing systems in that it is completely modular, allowing different components to be selected for optimal performance specific to the gene targets. Base editing has been demonstrated in T-cells and iPSCs using the Pin-point system, showing that the technology has potential across a range of cell types and therapeutic indications. Revvity has also developed a novel proprietary method to leverage the base editing mechanism to insert genes, such as to create an allogeneic CAR-T cell therapy by knocking in a CAR while knocking out immune markers simultaneously.

The Pin-point base editing system is part of Revvity's cell and gene therapy portfolio, which spans gene modulation and editing, cell analysis, immunoassays, and optimised AAV and lentiviral vector development and manufacturing to improve the specificity, efficacy and safety of cell and gene therapies. Solutions range from functional genomics assays, payload design, QA/QC, and vector optimisation through to characterisation, automation and process development to help customers achieve their cell and gene therapy research, development and manufacturing goals.

At Revvity, "impossible" is inspiration, and "can't be done" is a call to action. Revvity provides health science solutions, technologies, expertise, and services that deliver complete workflows from discovery to development, and diagnosis to cure. Revvity is revolutionizing what's possible in healthcare, with specialized focus areas in translational multi-omics technologies, biomarker identification, imaging, prediction, screening, detection, and diagnosis, informatics, and more.

With 2022 revenue of more than $3 billion and over 11,000 employees, Revvity serves customers across pharmaceutical and biotech, diagnostic labs, academia and governments. It is part of the S&P 500 index and has customers in more than 190 countries.

Alvotech & Advanz Pharma Extend Strategic Partnership to Commercialize Five Proposed Biosimilars in Europe

Alvotech and Advanz Pharma recently announced the companies have entered into an exclusive partnership agreement regarding the supply and commercialization of five biosimilar candidates in Europe. Alvotech will be responsible for development and commercial supply and Advanz Pharma will be responsible for registration and commercialization in Europe.

"We are very excited to extend our existing partnership with Advanz Pharma into additional therapeutic areas. The growth of our collaboration is based on a common vision and commitment to provide better patient access to more affordable biologics," said Robert Wessman, Chairman and CEO of Alvotech.

"This partnership positions Advanz Pharma as a key future player in European biosimilars. It is also an important next step in Advanz's ambition to be a partner of choice for the commercialization of specialty, hospital, and rare disease medicines in Europe," added Steffen Wagner, CEO of Advanz Pharma.

Anil Okay, Chief Commercial Officer of Alvotech, also added "After signing our initial partnership agreement with Advanz earlier this year, we look forward to deepening our relationship and working with Advanz on bringing additional important therapies to market in Europe."

Susanna El-Armale, Chief Corporate Development Officer at Advanz Pharma, said "This strategic partnership with Alvotech materially strengthens Advanz's pipeline of specialty pharmaceuticals to drive mid- and long-term sustainable growth."

The agreement includes candidate biosimilars to Simponi (golimumab) and Entyvio (vedolizumab) and also includes three additional early-stage, undisclosed biosimilar candidates. According to IQVIA, the current addressable market for these five biosimilars is more than $4 billion for the markets in scope of the agreement.

In February 2023 Alvotech and Advanz Pharma announced that the companies had entered into an exclusive agreement for the commercialization of AVT23, a proposed biosimilar to Xolair (omalizumab). The agreement covers the European Economic Area, UK, Switzerland, Canada, Australia, and New Zealand.

Alvotech is a biotech company, founded by Robert Wessman, focused solely on the development and manufacture of biosimilar medicines for patients worldwide. Alvotech seeks to be a global leader in the biosimilar space by delivering high quality, cost-effective products, and services, enabled by a fully integrated approach and broad in-house capabilities. Alvotech's current pipeline includes eight disclosed biosimilar candidates aimed at treating autoimmune disorders, eye disorders, osteoporosis, respiratory disease, and cancer.

Partner of choice in specialty, hospital, and rare disease medicines. Advanz Pharma is a global pharmaceutical company with the purpose to improve patients' lives by providing and enhancing the specialty, hospital, and rare disease medicines they depend on. Our headquarters are in London, UK. We have commercial sales in more than 90 countries globally and have a direct commercial presence in more than 20 countries, including key countries in Europe, the US, Canada, and Australia, a Centre of Excellence in Mumbai, India, as well as an established global distribution and commercialization partner network.

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Formulation Forum

PLGA – A Versatile Copolymer for Design & Development of Nanoparticles for Drug Delivery

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

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INTRODUCTION

Poly (lactic-co-glycolic acid) or PLGA, a highly hydrophobic copolymer composed of lactic acid and glycolic acid, has been approved in many drug products and medical devices.[1] Throughout the years, since first approved in 1997, PLGA has been a widely studied polymer in the industry because of its compatibility and safety.[2] As a homopolymer of two polymerized acidic moieties, one is relatively a hydrophobic lactic acid, and the other is a hydrophilic glycolic acid. PLGA with its unique LA/GA composition ratios and molecular weight provides a good barrier to protect the premature release and degradation of drugs encapsulated in microspheres or nanoparticles. Because of its biocompatibility and biodegradability in nature, it also has been used in several oncology drugs.[3]

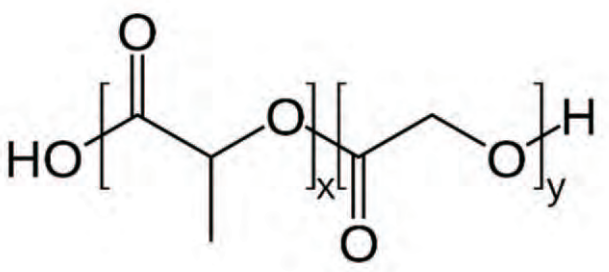
The following will focus on the chemistry, properties, applications, and regulatory aspects of PLGA, and the future trends in the industry, especially those requiring the development of long-acting injectables for the treatment of a variety of rare diseases and for life cycle management.

STRUCTURE OF PLGA

PLGA is synthesized by ring-opening chemistry that follows the copolymerization of a monomer of lactic acid and glycolic acid moieties. PLGA is a polyester in which these moieties are linked together by ester linkages to a linear aliphatic polymer as shown in Figure 1.

Different grades of PLGA are commercially available for pharmaceutical applications as microspheres, nanoparticles, and medical devices. Depending upon the molar ratios of lactic acid and glycolic acid used in the synthesis, the PLGAs used for pharmaceutical applications are composed of 75% lactic acid and 25% glycolic acid and/or 50% each of lactic acid and glycolic acid. PLGA, with its lactic acid and glycolic acid molar ratios of 75:25, 50:50, or 85:15, exists in an amorphous state.[4] PLGA (Tg 40°C-60°C) is typically soluble in a wide range of chlorinated methylene chloride chloroform, and hexafluoro isopropanol (HFIP) and non-chlorinated solvents, such as THF, acetone, DMSO, glycofural, ethyl acetate, ethanol, N-methyl pyrrolidone, methyl ethyl ketone, acetonitrile, isosorbid dimethyl ether, dioxane, among others.[5] In water, PLGA biodegrades by hydrolysis of its ester linkages. The methyl side group in poly lactic acid moiety makes it relatively more hydrophobic than polyglycolic acid, and hence, lactide rich PLGA copolymers are less hydrophilic and susceptible to degradation by hydrolysis.[6] Faster degradation depends on the ratios of the two acids; the higher the lactic acid, the slower the degradation and vice versa. In LA/GA 1:1 copolymer, the degradation is fast, leading to formation of lactic acid and glycolic acid within 3 months. Lactic acid is metabolized in tricarboxylic acid cycle and gets excreted via carbon dioxide and water, whereas, glycolic acid metabolizes the same pathway as lactic acid, and it gets excreted through the kidneys. Glycolic acid is also metabolized into oxalic acid, which may

FIGURE 1



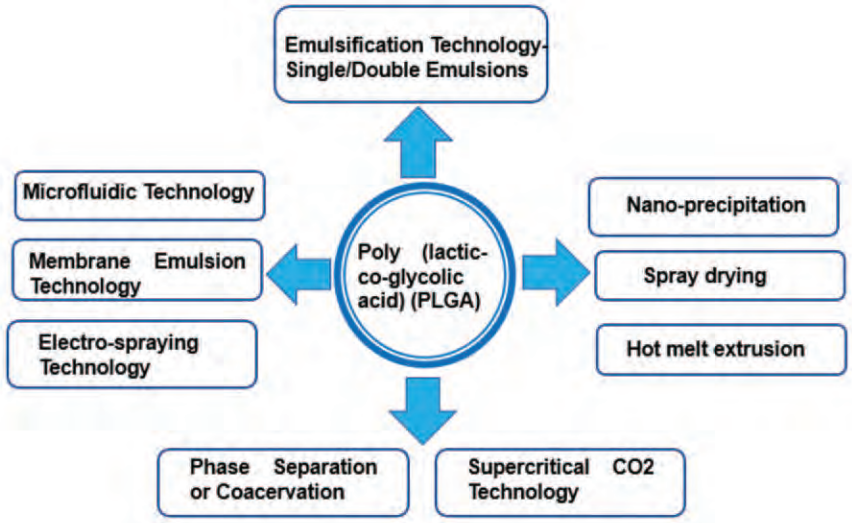
Structure of PLGA: Poly (lactic acid-co-glycolic acid (x= lactic acid and y = glycolic acid units).

lead to systemic toxicity in the body during implantation or longer circulation of PLGA microspheres.

CHARACTERISTIC & DRUG DELIVERY OF PLGA MICROSPHERES

Physico-chemical properties of PLGA, such as molecular weight, LA:GA copolymer ratios, crystallinity, nature of drug, and its loading, as well as the particle size, morphology and porosity of the nanoparticles may affect the in vitro drug-release characteristics.[7] The challenges in utilizing PLGA stems from encapsulating hydrophilic drugs into hydrophobic PLGA. The challenges with reducing burst release and increasing encapsulation efficiency of hydrophilic drugs in PLGA require additional functional hydrophilic layers. To overcome this issue, additional functional layers, like hydrophilic gels/hydrogels around the PLGA core-shell microspheres for sustained release are used. Yu et al demonstrated losartan-loaded PLGA microspheres with gel cores along the exteriors yielded high encapsulation efficiency of water-soluble drugs.[8] By selecting 5% gelatin in the inner core, release was more than 30 days compared to 16-day release with water in the inner cores. With 25% Poloxamer 407 as a hydrogel, it showed initial slower release, but as P407 swelled, microcapsules cracked resulting in faster release of drugs. In other cases in which Poloxamer 407 hydrogel can encapsulate small molecules like goserelin, a hydrophilic peptide, and acts as a hydrogel depot at the exterior, PLGA depot encapsulated with the same drug prepared via the double emulsion solvent evaporation method resulted in a combined encapsulation efficiency of >94%. The resulting di-depot structure with PLGA and Poloxamer 407 showed 2-week controlled release, first diffusion of drug through PLGA core followed by diffusion of drug through Poloxamer 407 core.[8]

FIGURE 2



Processing Methods for Fabricating PLGA Microspheres and Devices

PLGA microsphere's core shells are distinct in nature, and depending upon the usage of these nanoparticles, they may have varying core shapes, internal structures, shell thicknesses, and morphologies and porosities.[9] The latter is most explored for designing and increasing drug loading in PLGA microspheres for controlling the delivery by changing the porosity of the PLGA cores. Pore size and porosity of PLGA microspheres with broader surface area and lower density play an important role in faster releasing of drugs.[10] A number of porogen agents, such as sodium chloride, ammonium bicarbonate, a tri-block copolymer Poloxamer 407, sodium oleate, gelatin, bovine serum albumin, cyclodextrins, and mineral oils have been investigated for creating porous PLGA microspheres. Porosity can be modified by solvents and polymer concentrations. For example, solvents with lower boiling points, the pores are larger and vice versa.[11] Likewise, increasing the polymer concentrations from 1% to 5%, the porosity decreases about 25%.[12] Other porogen agents have also been studied. For example, Qutachi et al prepared porous PLGA microspheres with an average size of 84 microns and pore size of 8 microns-15 microns by treatment for 2 mins with ethanolic sodium hydroxide (EtOH/NaOH) and used as injectable cell carriers.[13]

PREPARATION OF PLGA MICROSPHERES & DEVICES

Ruirui et al describe some of these methods used for delivery of a number of drugs encapsulated in PLGA micros/nano-spheres.[14]

Emulsion and double emulsion solvent evaporation process - (W/O/W) – this process is simple and requires the drug to dissolve in an aqueous solution (W) with or without excipients, and the PLGA is dissolved in organic solvents, preferably in methylene chloride or ethyl acetate (O). First W/O emulsions are formed by adding and mixing of aqueous solution of drug in PLGA dissolved in organic solvent. The first emulsions (W/O) are then mixed with a second continuous aqueous solution containing a surfactant, such as polyvinyl alcohol (PVA) to yield W/O/W emulsions. Following removal of organic solvent through diffusion or extraction or evaporation, it leads to solidification of the PLGA microspheres.

Phase separation or coacervation method - This requires the preparation of first emulsions by addition of aqueous drug into PLGA dissolved in methylene chloride. A coacervation agent, such as silicon oil, is gradually added into primary emulsions to promote phase separation. As methylene chloride is extracted into the silicon oil, PLGA microspheres get precipitated, which are further hardened by washing with apolar solvents, such as heptane or hexane.

Spray drying process - This atomization-based process requires the spray drying of W/O emulsions prepared by aqueous drug mixing with PLGA dissolved in methylene chloride. The resulting spray dried powder of PLGA microspheres entrapped with drug are dried to remove the residual solvents.

Hot melt extrusion (HME) - Hot melt extrusion is an ideal solvent-free method for creating implants by processing of PLGA at temperatures higher than glass transition temperature (T_g) of polymers, PLGA/PLA. The resulting extrudates or rods can be used as implants.

Nano-precipitation method - This process requires dissolving drug and PLGA in water-miscible organic solvents and injecting into an aqueous-phase water that leads to solvent exchange by diffusion and nanoprecipitation of drug into PLGA depots, ideally suited as reservoirs for in situ delivery.

Supercritical CO_2 method - It involves the injection of drug dissolved in methanol into SC-CO_2 as an anti-solvent, which acts as an extractant for methanol, and instantaneously lead to precipitation of drug nanoparticles, which is encapsulated in PLGA with well-dispersed drug in microspheres.

Electro-spraying process - It is based on atomization of drug and PLGA in an organic solvent, which is subjected to electric voltage to produce the particles. It is commonly used in preparation of solid dispersions of poorly soluble drugs.

Microfluidics technology - It offers good controls over particle size distribution and is amenable to low volumes. Microfluidic systems fitted with 1-mm channels have shown to be suitable for large-scale production of PLGA nanoparticles.

Membrane emulsification technology - It is relatively a new technology that employs a combination of emulsification methods and porous membranes in which the dispersed phase is pressed through a membrane, and the droplets formed are carried away with the continuous phase, which results in more uniform and controlled particle size with narrow distribution and high drug encapsulation efficiency than emulsification solvent evaporation technology.

PLGA NANOPARTICLES IN DRUG DELIVERY OF BLOOD BRAIN BARRIERS

The blood brain barrier (BBB) protects the central nervous systems (CNS) from unnecessary entry of unwanted substances, which also pose challenges in delivery of molecules for treatment of glioblastoma and other diseases in the brain. These tight junctions (TJs) formed by a complex network of proteins and linked with the cytoskeleton can restrict the passage of substances from the bloodstream to the brain, and as a result, many of the therapeutic agents can't overcome the BBB. Kabanov et al have shown that poloxamer micelles (hydrophobic in nature) can penetrate the BBB and deliver the drugs.[15] PLGA nanoparticles (hydrophobic in nature) can penetrate the BBB and can be used as carries for delivery of drugs.[16] PLGA NPs with surface-modified surfactants also improved the cellular uptake by permeation of BBB. For example, PLGA NPs coated with vitamin E-TPGS, poloxamer 188, and polysorbate 80 improved the cellular uptake due, in part, to changes in

TABLE 1

NPs	Size (nm)	Admin	Dose (mg/ml)	Drug	Animal Model	Brain Uptake, %					
						0.5 h	1 h	1.5 h	3 h	6 h	12 h
1% PS80/PLGA	138	oral	100/200/400	estradiol	Rats	-					
4% PS80/PLGA	157	oral	100/200/400	estradiol	Rats						
PS80/PLGA	194	i.v.	20	EF	Rats	4.3					
TPGS/PLGA	165	i.v.	20	EF	Rats	4.2					
P407/PLGA	188	i.v.	20	EF	Rats	5.5					
P188/PLGA	196	i.v.	20	EF	Rats	6.2					
P188/PLGA	252	c.a.	5000	EF	Rats	3.2					
PS80/PLGA	231	c.a.	5000	EF	Rats	6.4					

c.a. carotid artery; EF entrapped fluorescence marker; PS 80- Polysorbate 80, TPGS-Vitamin E-TPGS; P188 – Poloxamer 188; P407 – Poloxamer 407; iv. Intravenous route

Brain uptake of surface-modified PLGA

surface hydrophilicity and surface charge.[17] The MDCK cellular uptake of TPGS-coated PLGA (222 nm) was 1.5-fold higher compared to PVA-emulsified PLGA NPs following 4 hours of incubation. Likewise, with Poloxamer 188 and PS80-coated loperamide-encapsulated PLGA nanoparticles, the in vitro cellular uptake was 21% and 14.5%, respectively, compared to 4.5% uptake with unmodified PLGA nanoparticles with respect to free drug (ca. 0.4%). In vivo uptake differed considerably compared to in vitro cellular uptakes. Table 1 lists the brain uptake of surface-modified PLGA nanoparticles in animal models.[16]

It is evident from Table 1 that carotid administration showed relatively higher brain uptake than intravenous route of administration. For example, PS80-coated PLGA (231 nm) was delivered relatively higher than P188-coated PLGA nanoparticles (3.2%) at the same dose level by carotid route of administration in an hour. In other studies, P188 surface-modified PLGA nanoparticles were found to be better BBB targeting than PS 80 following intravenous administration.[17]

REGULATORY INFORMATION ABOUT PLGA & DRUGS APPROVED BY THE FDA

PLGA regulatory status is well established.[18] It has been approved in many drug products (Table 2).[19]

PLGA is also listed in the FDA's inactive ingredient database. Table 3 shows PLGA (free acid terminal) has been approved as implants and also in injectable solutions and suspensions for intravitreal, subcutaneous, and intramuscular drug products with maximum potency per unit and/or maximum daily exposure (MDE) limits. Evidently, the amounts of polymer could range from 135 mg to 533 mg per unit depending upon the formulation dosages to 11 mg-145 mg to MDE as injection suspension powders.[20]

TABLE 2

Drug	Active	Indication	Duration/Dose
Lupron® Depot	Leuprolide acetate	Prostate cancer	1-6 m/7.5-45 mg
Eligard®	Leuprolide acetate	Prostate acetate	1-6 m/7.5-45 mg
Bydureon®	Exenatide	Type 2 Diabetes	1-w/2.0 mg
Trelstar®	Triprorelin pamoate	Prostate cancer	1-3-m/3.75-22.5 mg
Sandostatin® LAR	Octreotide acetate	Neuroendocrine tumor	1 m/20-30 mg
Signifor® LAR	Pasireotide pamoate	Acromegaly/cushing disease	1 m,10-60 mg
Zoladex®	Goserelin acetate	Prostate, breast cancer	1-m, 3 m/3.6 mg,10.8 mg
Superfact® Depot	Buserelin acetate	Prostate cancer	2 m, 3 m/6.3 mg, 9.5 mg
Arestin®	Minocycline HCl	Antibiotic	1 mg

PLGA-based approved drugs.

ASCENDIA'S CAPABILITIES IN PLGA NANOPARTICLE FORMULATIONS

PLGA has been investigated in long-acting injectable formulations of a number of drug products from early phase to clinical phases of development. Ascendia's in-house capabilities in upstream and downstream cGMP manufacturing of injectable lipid-based LipidSol® and polymeric-based PLGA have been well utilized within our state-of-the art sterile facility with ISO-certified cleanrooms. Table 4 shows the preparation of carvedilol- loaded PLGA nanoparticles from PLGA (50:50 LA/GA).[21]

The method for preparation of carvedilol-encapsulated PLGA nanoparticles involves dissolving the drug and polymer (1:10) in methylene chloride by thorough mixing as an oil phase. An aqueous solution containing 2% polyvinyl alcohol (PVA) with MW 9,000-10,000 D was used as a surfactant. API/polymer oil phase was added slowly in PVA aqueous solution dropwise and mixed thoroughly, keeping the oil/water phase ratio 1:7. The entire solution was mixed thoroughly in ice cold water to emulsify by sonication (Fisher Scientific Sonic Dismembrator Model 500) to achieve the desired particle size (Malvern Nano-ZS zeta sizer). The resulting nanoparticles were poured and mixed in 2% PVA aqueous solution for 3 hours, and collected following the centrifugation for 30 mins at 14,000 xg. The drug/PLGA nanoparticles were collected by discarding the supernatant and washed repeatedly with water. The resulting pure concentrated drug/PLGA nanoparticle suspension once again was passed through filter (Amicon® Ultra Centrifugal filter with MW 50 kD cut off), and centrifuged again for 10 mins at 14,000 xg to remove any free drug. It was lyophilized with sucrose (10%-30%) as cryo-protectant or used freshly or stored at 4°C for weeks, and drug loading was determined by HPLC, and release profile of drug was assessed.

TABLE 3

Inactive Ingredient	Route	Dosage Form	Max. Potency/Unit	Max. Daily Exposure
DL-Lactide & Glycolide (50:50) copolymer 12000 Acid	Endosinusial	Implant	1.35 mg	
DL-Lactide & Glycolide (50:50) copolymer 12000 Acid	Intravitreal	Implant	116 mg	
DL-Lactide & Glycolide (50:50) copolymer 12000 Acid	Intravitreal	Injection	116 mg	
DL-Lactide & Glycolide (50:50) copolymer 12000 Acid	Subcutaneous	Injection, Solution	533 mg	
DL-Lactide & Glycolide (75:25) copolymer 20000 Acid	Intramuscular	Injection		145 mg
DL-Lactide & Glycolide (75:25) copolymer 20000 Acid	Intramuscular	Injection, powder, for suspension		11 mg

PLGA listed in IID database (as of May 2023)

TABLE 4

Polymer	MW D	Viscosity dL/g	T_g, °C	Half Life	Surfactant	Particle Size nm	Zeta Potential mv
PLGA/50:50	7000-17,000	0.16-0.24	42-46	< 3 mo.	2% PVA	128 nm	-13.4
PLA (Reference)	18,000-24,000	0.25-0.35	48-52	< 6 mo.	2% PVA	135 nm	-11.4

PLGA vs PLA Nanoparticles: Physico-Chemical Properties

SUMMARY

PLGA is widely used as an alternative drug delivery system for injectable drugs as a long-acting excipient. It forms microspheres that allows slow or control release of drugs. It is biocompatible and biodegradable, which makes it attractive for pharmaceutical drugs and medical devices. It is hydrophobic in nature with the ability to help hydrophobic drugs with limited ability for encapsulation of hydrophilic molecules. However, co-encapsulation with hydrophilic and hydrophobic drugs with high encapsulation efficiency is possible by changing the composition of the microsphere core-shell. Surface modification of PLGA with PEG or receptors can lead to longer circulation and targeting of certain disease tissues, respectively. PLGA microspheres can increase drug loading and avoid phagocytosis by macrophages, thus achieving a longer lasting drug-release effect. Because of their smaller particle size and targeting characteristics, they are easier to accumulate in tumor cells through the enhanced permeability and retention (EPR) effect. In addition to therapeutic molecules, imaging agents can also be encapsulated in w1/o/w2 double emulsions to help improve cancer cells targeting and bioavailability of hydrophobic molecules. Choice of selecting non-toxic solvents also adds another significant step forward to select PLGA for designing a safe vehicle for encapsulating and delivering drugs across all modalities. Designing PLGA micro/nanospheres requires smarter selection of the fabricating process. For example, membrane emulsion and microfluidics methods yield PLGA microspheres with higher drug encapsulation efficiency and with lower polydispersity index, for example, PDI of 0.048 with carvedilol encapsulated PLGA.[21] Taken collectively, Ascendia's capabilities in the downstream and upstream manufacturing process can lead to development of PLGA-based nanoparticle-encapsulated drugs for life-threatening ailments. State-of-the-art cGMP manufacturing suites designed to handle organic solvents, including methylene chloride, are well in place for future generations of polymeric and lipid-based nanoparticles for unmet medical needs. ◆

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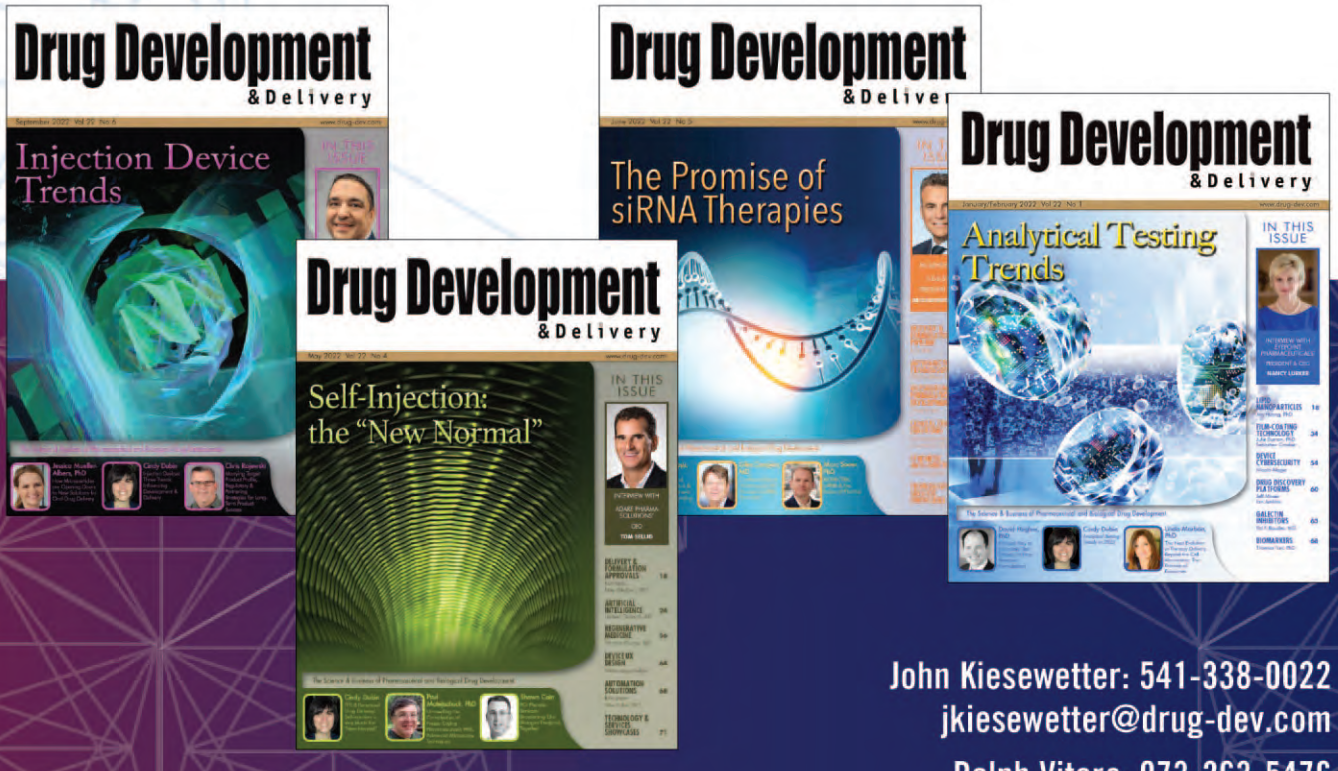

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DRUG DEVELOPMENT

Overcoming Challenges on the Path From Candidate Selection to First-in-Human Clinical Testing

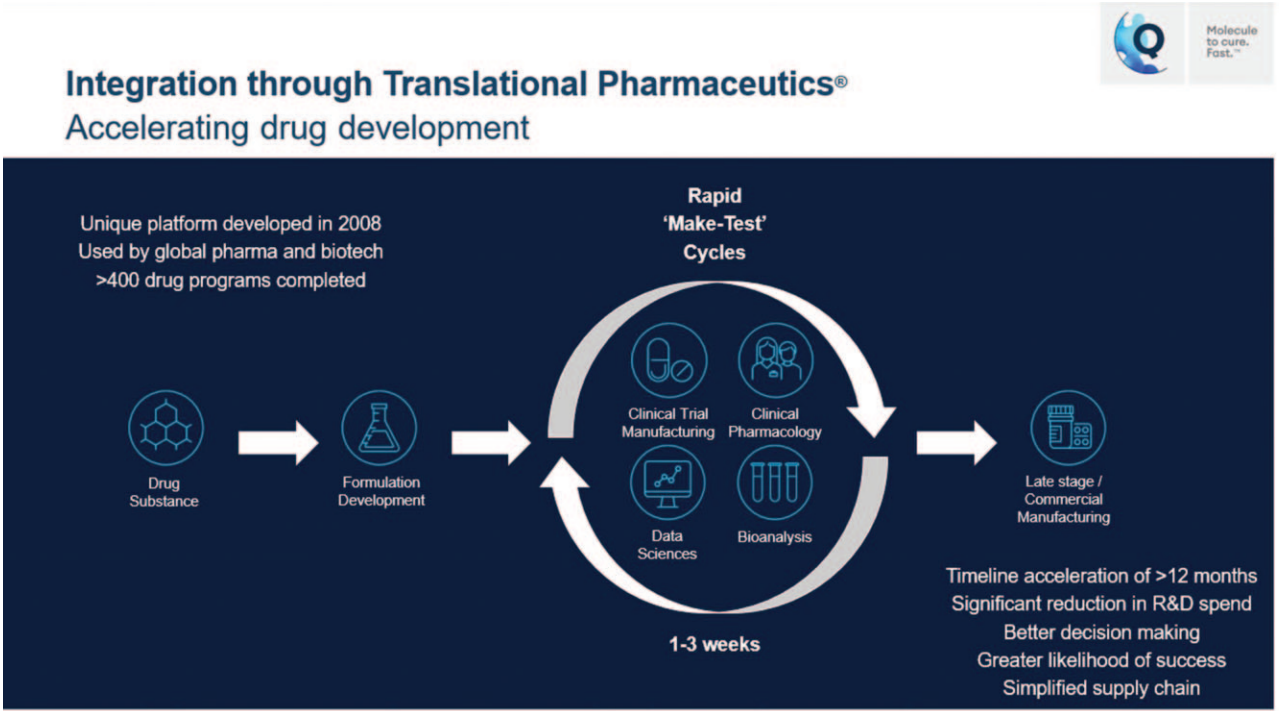
By: Eleanor Row, PhD

TRENDS IMPACTING DRUG DEVELOPMENT PIPELINES

A key trend affecting all segments of the pharmaceutical market is the rising number of drugs in the development pipeline seeking to treat rare and orphan diseases. By 2026, orphan drug sales will account for a fifth of all prescription drug sales and almost a third of the total value of the global drug pipeline.[1] It is predicted that by 2026, the top 10 orphan blockbusters will be worth between $3 billion and $13 billion each, outgrowing the mass market drug segment.[2]

The new focus on devising treatments for rare diseases has resulted in an increased interest in highly potent active pharmaceutical ingredients (HPAPIs) as drug candidates. These are small molecule drugs that produce a response or pharmacological effect at a very low dose, which offers a potential benefit for patients, especially in the area of oncology and treatment of other serious diseases. The global HPAPI market was estimated to be worth $24.5 billion in 2022, and is projected to reach $39.6 billion by 2027, growing at a CAGR of 10.1% throughout the forecast period.[3]

With so many of these highly potent new chemical entities on expedited regulatory approval pathways, there is high demand for customers and contract drug development and manufacturing organizations (CDMOs) to meet ever-shorter timelines and reduce costs while avoiding common pitfalls on the pathway from candidate selection to FIH trial. Anticipating these hurdles is vital if companies wish to succeed in avoiding them and accelerating their project to the trial stage.



UNDERSTANDING THE CHALLENGES FACING COMPANIES TRANSITIONING FROM CANDIDATE SELECTION TO FIH

Regardless of the nature of the drug development project, pharmaceutical innovators face a number of challenges on their journey to reach their clinical trial. The key barriers to overcome include:

- **Finding the right molecule:** Identifying the optimum candidate to progress into clinical development is a complex process. Companies will invariably have a wide range of potential leads under investigation to determine not just their therapeutic efficacy, but also their commercial viability. Lead candidates must be ranked based on their specificity and selectivity for the biological target of the desired therapeutic area, in-vitro activity, as well as their early biopharmaceutical "developability."

- **Completing CMC development:** Having chosen an appropriate lead candidate, the next goal is to complete all of the necessary chemistry, manufacturing, and controls (CMC) development and safety studies that will support regulatory approval to begin a Phase 1 clinical trial in humans. Not only must the candidate present an acceptable pharmacokinetic profile and demonstrate in-vivo efficacy, it must offer a good safety pharmacology margin with an acceptable drug-drug interaction profile.

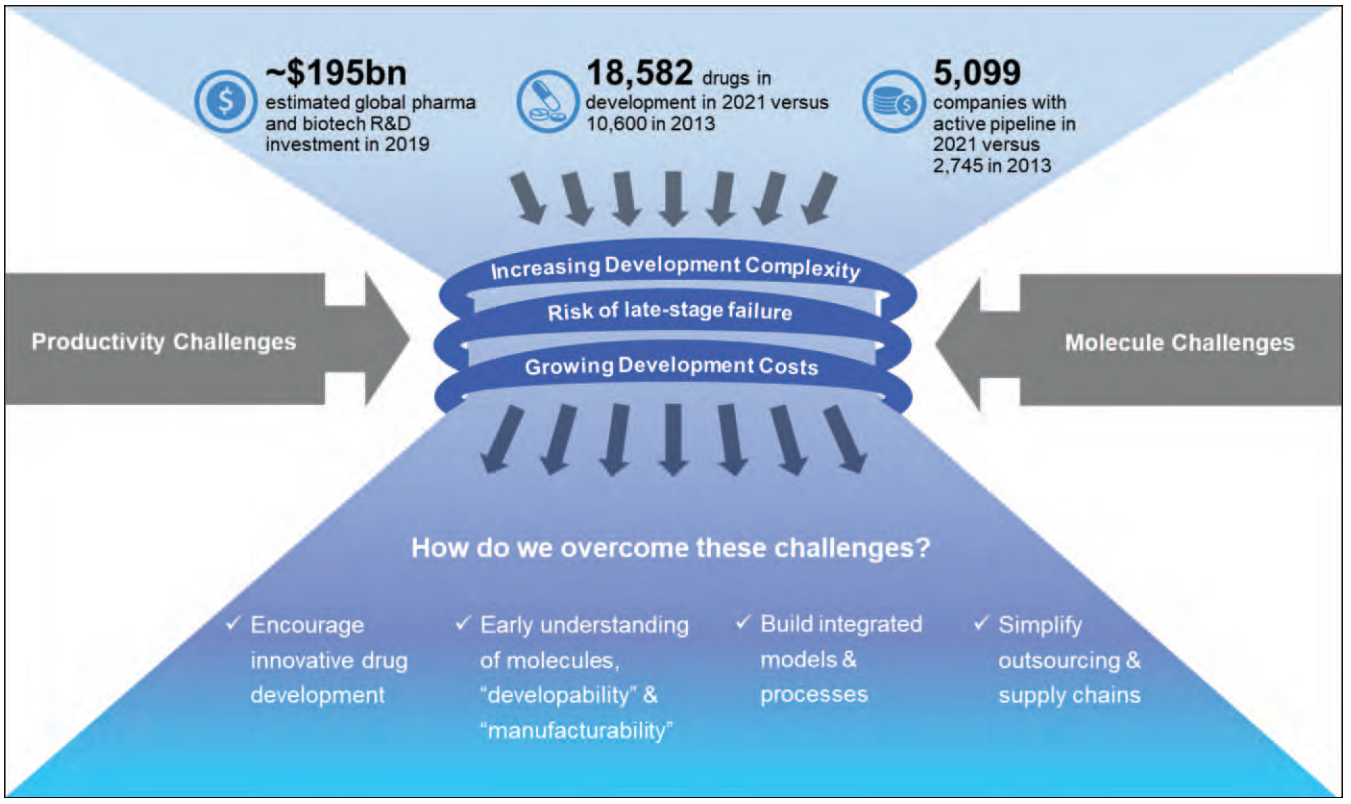
- **Accessing sufficient and flexible drug substance manufacturing capacity:** From the CMC stage onward, pharmaceutical companies must be able to acquire increasing quantities of their selected drug substance, as focus shifts from synthesizing small amounts of API from medicinal chemistry routes to the development of a scalable synthetic process. Pharmaceutical companies should also begin thinking about the provision of the first kilogram of good manufacturing practice (GMP)-grade material suitable for embarking on early clinical development.

Failure to navigate these challenges effectively can delay or - in the worst-case scenario - derail the project, so it is important for the work to be undertaken with the utmost care, ideally with expert support and specialist infrastructure.

KEY CONSIDERATIONS WHEN DEVELOPING A DRUG SUBSTANCE MANUFACTURING PROCESS

Optimization of the synthetic route is crucial to the successful development of an effective and efficient drug substance manufacturing process. This must be done as early in the development process as possible; changes to the route at a later stage can be time-consuming and costly. Additional bridging toxicology studies may also need to be produced to confirm the impact of any differences in the impurity profile of the candidate.

A robust and commercially scalable synthetic process design can support com-



profile of the candidate.

A robust and commercially scalable synthetic process design can support companies in avoiding many of the common issues that can add risk to material supply. Even at this early phase of development, it is important to optimize the synthetic process by minimizing the number of steps. This can be done by telescoping or identifying commercially available starting materials with a robust supply chain, developing simple purification and isolation strategies, or eliminating the use of hazardous reagents or intermediates (particularly genotoxic impurities).

Considering the potential impurities that can be produced when synthesizing the candidate is vital. By performing analytical method development in parallel with the development of the synthesis, allows for impurities to be readily identified and quantified. This can give pharmaceutical companies an in-depth understanding of the impurities from a very early stage of development so they can identify appropriate control points within the synthesis. It can provide invaluable insight to enable companies to reduce timelines, enabling non-GMP demonstration batches to be started as soon as the synthetic methodology is available. Moreover, it can accelerate the initiation of stability studies once material is available to support the clinical shelf-life and pivotal data for the CMC dossier submission.

THE IMPORTANCE OF DEVELOPING A REGULATORY STRATEGY FROM THE BEGINNING OF THE PROJECT

It is never too early to begin considering and devising a comprehensive long-term regulatory strategy, nor to identify potential GMP starting materials appropriate to for downstream product development. Regulatory starting materials should be selected to allow a sufficient number of manufacturing stages to be performed under GMP to demonstrate to regulators there is optimum drug substance quality control.

Changing starting materials at a later stage in clinical development to meet more stringent regulatory requirements may increase costs and cause unnecessary delays. This is because additional clinical studies may be needed to prove that changes in starting materials do not change the toxicology or impurity profiles of the final material.

OTHER KEY FACTORS DRUG PRODUCT & CMC TEAMS SHOULD BE AWARE OF AT THIS STAGE

Something often overlooked during early development is the selection of the right physical form for the drug substance. Making the right decisions early can lead to a more robust drug substance isolation strategy and formulation, which can result

in significant reductions to drug product development timelines.

By defining the desired salt form (or free form) of the molecule earlier in the project, pharmaceutical companies don't need to carry out bridging toxicology or stability studies further downstream. This can reduce cost and streamline later development processes. Defining the physical form this early also puts product sponsors in a much stronger intellectual property position when patenting their discoveries.

Understanding the physical form and the molecule's behavior is also crucial when trying to design a formulation for the clinic. Technology selection is dependent on the solubility and permeability of a compound utilizing the Developability Classification System (DCS). With this in mind, the sooner this data is available to a formulation team, the shorter the lead time to a developed formulation.

Using a relatively simple "fit-for-purpose" formulation is a tried and tested solution during an early clinical evaluation program that provides a number of important benefits by minimizing time and expense compared with alternative strategies. In addition, it provides significant flexibility in terms of manufacturing varying numbers of doses for administration during early clinical trial programs where, due to their nature, dosing regimens have not yet been fully defined.

THE VALUE OF ENGAGEMENT BETWEEN CHEMISTRY, CMC & CLINICAL GROUPS AT THE EARLY STAGE OF DEVELOPMENT

It is not uncommon for drug substance, drug product, and clinical activities to be carried out by separate contract development organizations. If these companies don't collaborate successfully, the overall development process can become inefficient and costly. It may result in poor knowledge and material transfer as the project progresses along the development pipeline, which can increase the risk of delays in hitting key milestones.

However, there are CDMOs with the expertise and specialist infrastructure to offer integrated drug substance, drug product, and clinical testing activities, all under a single organizational umbrella and one program manager.

By offering such a fully integrated approach to drug development, these CDMOs bring together process development, analytical, and formulation development chemists who collaborate regularly from the outset of the project. Data and drug substance information can be freely shared, meaning activities usually only initiated on completion of the drug substance program can begin several months earlier.

On average, drug development timelines can be cut by up to 6 months in the candidate development stage by utilizing an integrated approach, which translates into significant R&D cost savings. An integrated development partner that offers regulatory insight and expertise can also help ensure a smooth review by regulators, accelerating clinical trial approval. The overall benefit is a significant reduction of drug development timelines from candidate selection to clinical development, enhancing the likelihood of clinical and commercial success and reducing the overall program risk.

FOCUSING ON TODAY'S DEVELOPMENT CHALLENGES IS CRUCIAL, BUT DON'T LOSE SIGHT OF FUTURE ISSUES

As a molecule approaches the transition to a FIH clinical trial, there are many unknowns that will influence its future success. What this success looks like in clinical terms will depend on the early establishment of efficacy, with the current trend being to bring patient investigations into the first clinical protocol.

However, the practicalities of enabling such a study design can often result in a significant deceleration for the first-dose-in-human milestone.

Clinical operations teams therefore shouldn't just focus their attention on answering the current critical questions in their molecule's development. They should also be aware of the needs of future pivotal efficacy investigations, but not allow them to delay the collection of decision-making data in the moment.

INTEGRATING DEVELOPMENT WORK IS KEY TO ACCELERATING A MOLECULE'S PATH TO CLINICAL TRIAL

Product sponsors can face many challenges when progressing their project from drug discovery into preclinical and clinical development, especially for rare and orphan diseases and those harnessing new and untried HPAPIs. It is not uncommon for them to have to split their program across multiple service providers. This places the project management burden on the sponsors, rather than their outsourced partners. It creates white space in the development timeline, limits knowledge and

material sharing, and ultimately increases costs and the risk of delays.

By working with a partner, such as Quotient Sciences, capable of offering a fully integrated development service from candidate selection through to FIH clinical trial under our unique Translation PharmaceuticsTM platform, both pharma and biotech companies can benefit from holistic scientific advice and recommendations. They can work with multidisciplinary project teams offering unique CMC, clinical, and biopharmaceutical know-how and capabilities all within one team. This can streamline the management of their project as they only have to deal with one contact and one working culture. Through tight integration of early development activities under a single organization, it is possible to cut through traditional industry silos. As a result, companies can accelerate their development timelines, even for rare and orphan diseases, ultimately enabling them to get their innovations to the patients that need them most. ◆

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BIOGRAPHY

Dr. Eleanor Row is Executive Director, Candidate Development at Quotient Sciences. She has more than 16 years of experience in the pharmaceutical and contract research environment working with multinational companies, such as Sanofi-Aventis and Covance. She earned her PhD in Chemistry/Pharmacology from The University of Sheffield. Her subsequent post-doctoral studies were carried out at the University of Liverpool under the supervision of Dr. A. Stachulski and Professor P.M. O'Neill developing anti-parasitic and anti-malarial compounds. In 2006, she moved to Sanofi-Aventis, focusing on the synthesis of radio/stable labelled compounds and has a proven track record for delivering high-quality materials to sponsors. Dr. Row has held a variety of Senior Leadership roles and as an APM-accredited Project Manager, has first-hand experience of leading early candidate development programs.

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Chris Preti
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The Importance of Expertise in Sterile Fill Finish

Sterile injectable manufacturing requires much more than available capacity and equipment – although those are important. This critical stage of the drug manufacturing process, when outsourced, calls for a contract manufacturing organization (CMO) that can prove its value in the following key areas: product/molecule range, regulatory and compliance, cross-functional support, agile tech transfer, strong project management for maximum safety and quality, efficient production, and overarching commitment to customer success.

Drug Development & Delivery recently interviewed Chris Preti, President of Jubilant HollisterStier, to discuss how the CMO is handling increased demand for sterile fill finish and how expertise makes a difference to customer relationships and finished product quality.

Q: Jubilant HollisterStier proudly asserts its expertise in fill finish manufacturing, a critical stage in biopharmaceutical production. How does JHS distinguish itself as an outsourcing partner?

A: Our mantra is to be a customer-focused, high-quality, full-service CMO. We are uniquely focused on sterile fill finish of liquids and lyophilized injectables and also ophthalmic manufacturing and packaging solutions. This singular focus on fill finish has allowed us to build expertise that today benefits our customer base, from big and small-to-mid-sized pharma to biotech and specialty companies across 40 countries. While narrow in what we do, we're quite broad in our offering – handling both aseptically filled and terminally sterilized products, whether small molecule, biologics protein-containing products, liposomes, oligonucleotides, complex formulations, cold kits for radiopharmaceuticals, or vaccines. Our employees are skilled and knowledgeable in very specific manufacturing processes and bring that expertise to every project. They're able to anticipate challenges and provide solutions based on that expertise, which results in smoother, faster manufacturing processes for our customers. We pride ourselves on white-glove project management. Having joined as president just this year,

my goal is to bring forward this focus on expertise, superb full-service customer service, and quality as key differentiators for Jubilant HollisterStier. When I see that many of our customers have been with us for 5 and 10 years, and expand their product portfolio with us, that tells me our singular focus and attention to quality are meaningful to our customer relationships.

Q: It's said that fill finish is a common bottleneck in vaccine manufacture and deployment. Why is that, and how are you, as a contract manufacturer, removing friction from this stage?

A: Capacity constraints are well known throughout the industry and were, of course, heightened during Covid-19. But governments have also stepped up to partially fund capacity expansion projects, and Jubilant HollisterStier is a beneficiary of that at both our Spokane, WA, facility and our Montreal, Canada, facility. In the next 2 to 5 years, our own investments, in partnership with the US and Canadian governments, will double our capacity in both facilities and that will go a long way toward solving one kind of bottleneck. We're already taking orders for mid-2024 on a new high-speed filling line that features isolator barrier technology, single-use capabilities, up to 2,000-L batch size, 2mL-100mL fill capacity, and two lyophilizers.

Effective project management is also a difference-maker. Managing capacity and understanding what it will take to bring a product to fruition are skills that are earned over time – and our project managers have put in that time at Jubilant HollisterStier. We have a strong bench of experienced professionals leading our projects, from the tech transfer through regulatory approval.

Q: JHS has made significant infrastructure investments – in facilities and equipment – at your Spokane, WA, and Montreal locations. What was behind those investments? When do you expect them to be operational? And what has customer response been to these announcements?

A: We've undertaken a $285-million investment in our Spokane manufacturing facility. This is part of a cooperating agreement of $149.6 million with the US Government to expand critical domestic vaccine manufacturing capacity. This project doubles our capacity with two high-speed injectable fill lines with isolator technology and lyophilizers that will start taking production slots in mid-2024. We also recently announced a $78-million investment in our Montreal manufacturing facility that includes one new high-speed filling line (liquid and lyo) and additional investments to enhance our full-service ophthalmic offering for liquids, ointments, and creams. This is expected to be complete in 2026.

Customers are very enthusiastic and looking forward to expanding available projects as soon as we're ready.

Q: What did you learn from the Covid-19 pandemic, and what changes has this driven in your organization?

A: Covid taught us we can be even more agile and adaptable than we thought. Of course, there were a lot of contributing factors behind the speed with which vaccines were developed, manufactured, and distributed. But Jubilant HollisterStier responded to the call to manufacture and fill finish Covid-19 therapeutics in record time for six different customers. That wasn't without its challenges. Across the various projects, we had to re-engineer a complex process for FDA compliance; we dealt with cold chain supply issues and brought freezer trucks to our facilities; we worked supply chains hard to meet raw materials needs, and had to bring in or adapt certain equipment to keep pace with demand. Whatever it took, we were able to find a way forward. Our agility and expertise from tech transfer to bringing the products to market is one reason the US and Canadian governments chose to partner with us; we'd proven we could deliver.

Q: As the new president of JHS, what changes can customers expect from your leadership and vision for the company?

A: My goal is really to shine a light on the extraordinary talent and skill of our employees and the way they maximize their experience and our facilities and equipment to deliver what I like to call white-glove customer service from a customer-focused, high-quality, full-service CMO. Manufacturing is critical to achieving commercial success, and I'm delighted to be heading up an industry leader that's committed to providing the highest quality comprehensive services in partnership with our customers. Jubilant HollisterStier is a company with long-standing customer relationships, where we've maintained working partnerships with customers for a decade and longer, and continue to grow our engagements with them. That is the story we want to tell prospects, people who are looking not simply to get a project complete, but to have a great experience, to be confident in the process and the result, and know they are bringing a high-quality finished sterile injectable or ophthalmic product to market in the safest, most efficient, and cost-effective manner possible. ◆

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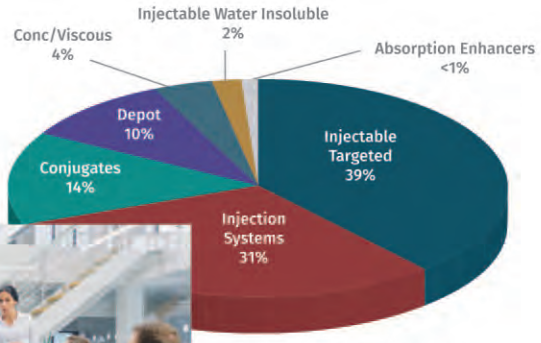

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Special Feature

Outsourcing Formulation Development & Manufacturing: Putting Customers First

By: Cindy H. Dubin, Contributor

The rising need for novel drugs to battle infectious and chronic diseases is one of the main drivers of the global formulation development and manufacture outsourcing market. Valued at $22.5 billion in 2021, the market is expected to skyrocket to more than $51 billion by 2031.[1] Higher R&D expenses, a desire to shorten time spent on these activities, and the fact that many companies lack the resources to perform these functions will only strengthen the contract sector.

Bio/pharma companies are being fairly warned by industry gurus that as drug substances continue to become more complex, the expertise and capabilities of contract development and manufacturing organizations (CDMOs) become more critical.

In this exclusive *Drug Development & Delivery* annual report, leading CDMOs from around the globe describe their unique development and manufacturing capabilities and technologies, and present real-world examples of how they have put these to use to produce innovative compounds, lower development costs, and shorten time to market.

Adare Pharma Solutions: Technology & Customer Focus Combined to Overcome Formulation Challenges

Adare Pharma Solutions is a technology-driven pharmaceutical CDMO that provides integrated end-to-end services to support the entire development of pharmaceutical products. Services include pre-formulation, phase-appropriate analytical and formulation development, QbD-based process development, clinical supplies, commercial manufacturing, and packaging.

According to Srinivasan Shanmugam, PhD, Adare Pharma Solutions' Senior Director of Pharmaceutical Sciences, Adare Pharma Solutions specializes in innovative oral solid dose technologies. "These technologies enable us to develop and manufacture unique dosage forms that serve the general patient populations as well as meet the unique needs of pediatric and geriatric patients," he says. "Our technologies can be combined and applied to a range of dosage forms, allowing us to develop more effective and efficient

A variety of oral dose forms developed and/or manufactured by Catalent.

drug products and overcome complex drug delivery challenges that other CDMOs may not be equipped to handle."

Adare Pharma Solutions takes a customer-centric approach toward providing CDMO services throughout the lifespan of a product. "This allows our customers to work with a single partner for all of their development and manufacturing needs, which can help streamline the development process and accelerate timelines," Dr. Shanmugam says. "Many of the same Adare experts can work closely with customers from a project's beginning to end, which allows for a deep understanding of a customer's specific needs and goals, as well as the ability to provide customized solutions engineered specifically to meet them."

A technology platform that Adare Pharma Solutions developed is the MMTS™ Multi Mini Tablet System. This customized release technology combines a tablet formulation with the flexibility of multiparticulate dosage forms and high drug-loading capability.

An example of Adare's MMTS technology and customer-centric culture combining to overcome a drug formulation challenge is the recent work with a medication for Exocrine Pancreatic Insufficiency (EPI). The customer wanted an alternate dosage option that would eliminate the need for patients to swallow several capsules a day, especially children and patients with cystic fibrosis. The formulation would also need to offer a broad dosage range for optimal symptom control.

"Working closely with the customer every step of the way, our scientists paired their API with our MMTS Minitabs technology, which resulted in a dosage form that could be sprinkled onto soft foods like applesauce and baby foods," Dr. Shanmugam explains. Adare scientists also demonstrated a broad dosage range from 3,000 to 40,000 USP units. "Additionally, MMTS Minitabs has likewise been shown to be very effective in gastronomy tube delivery, as potency remains unaffected while the Minitab beads deliver without sticking or clogging the tube."

Almac: Modifying to Meet Customer Needs

Almac Pharma Services is a CDMO with a focus on solid and liquid oral dose formulations. The company specializes in developing and manufacturing tablets, mini tablets, powders, capsules, solutions, and suspensions, from large-scale commercial production to smaller scale in support of clinical supplies, or orphan and niche commercial drug products.

"By offering a full range of services, including pre-formulation studies, process development, scale-up, validation, and ongoing commercial supply, we are able to offer a fully flexible single-service platform," says Sander van den Ban, Head of Technical Operations for the Almac Pharma Services Charnwood Facility. "We place a strong emphasis on quality and consistency, with a commitment to being able to solve complex formulation and manufacturing challenges and provide clients with a diverse and skilled team of experts."

Mr. van den Ban says the company has witnessed a growing trend in client's requesting high potency and pediatric small-volume high-complexity orphan or niche indications. "This is reflected in our tailored approach to client needs as we fully assess and partner with them to manufacture targeted medications," he explains. "We leverage equipment and product modelling approaches to guide our development as often timelines and API are heavily constrained. This provides an ability to reduce API and product waste, while also assessing scale-up needs, yielding a high reward for the client."

In recent years, he says there has been a shift in client needs as a growing desire has developed for more integrated services across the product lifecycle. As Almac provides a single-service offering, the company integrates from API development, formulation development, and manufacture, to clinical studies and on through to commercial supply. "A drug product can move through its lifecycle from one single source, continuously sharing knowledge between teams, resulting in complex development and manufacturing challenges being met with solutions based on learned product knowledge," he says. "Clients also benefit from reduced time and costs associated with coordinating multiple service providers."

Recently, a key client asked Almac to provide a solution that would enable the manufacture of a capsule containing oral granules (minitablets). Almac's current capsule filing machines were unable to meet that need as they were only equipped with powder and bead dosing units. Mr. van den Ban explains that Almac researched the best solution to fulfil the project requirements and ultimately chose to integrate the existing capsule filler with a universal tablet/micro-tablet feeding unit.

"This enabled us to satisfy the current production needs and fill minitablets into a capsule as per the selected recipe to achieve the required count," he says. "Not only were we able to provide a solution that met our client's needs, but we are able to provide this technology to our client base moving forward."

Ascendia: Taking the B.E.S.T. Approach to Liposome & Lipid Nanoparticle Formulation

Ascendia offers "one-stop-shop" CDMO services, leveraging its four core platform technologies to improve the solubility and bioavailability of a variety of modalities, with the notion "Making the Impossible Possible." Ascendia's proprietary nanotechnologies like Lipidsol, Nanosol, Emulsol, and Amorsol, can be applied to different molecules, small and large, including biologics.

Ascendia utilizes continuous manufacturing for lipid nanoparticle/liposome fabrication, offering scales from milliliters to hundreds of liters that meet the need of early- to late-stage development. "Coupling with microfluidic chip mixer, TFF, sterile filtration, and filling of single-use vial or prefilled syringe under aseptic conditions, we offer rapid turnaround of lipid nanoparticle development and manufacturing that bears the hallmarks of continuous manufacturing for sustained-release injectable (parenteral, intramuscular, and subcutaneous) drug formulations," says Shaukat Ali, PhD, Senior Director, Scientific Affairs & Technical Marketing, Ascendia Pharma, Inc. The company is also equipped with clean rooms, ISO 5, ISO 6, ISO 7, and ISO 8 for manufacturing of lipid nanoparticles and liposomes.

Utilizing its B.E.S.T. service philosophy, Ascendia functions as an integral CMC team member of its clients' drug development projects. This means that Ascendia proactively takes appropriate strategies to implement new technologies for innovative molecules, explains Dr Ali.

"More of the molecules being discovered are poorly soluble, making them challenging in development of suitable formulations due to their brick dust structures and high melting/logP," he says. "We overcome those challenges by first-hand screening of APIs in different excipients, solubilizer, and polymers listed in FDA's inactive ingredient database (IID) by utilizing our enabling technologies with aims to enhance the performance of these molecules."

Challenges also stem from drug instability resulting from degradation of APIs or lack of compatible excipients in the oral and parenteral formulations. Ascendia follows the decision trees based on the dosage forms and nature of the drugs, and select the most appropriate solubilizer and/or polymers in the formulations, he explains.

"We first identify prototype formulations that enhance bioavailability in animal models, and then further optimize the process and formulations leading to the next step of drug development in human clinical trials," Dr. Ali says. "Our expertise in lipid nanoparticles, liposomes, and surfactant-based nanoemulsions and microemulsions and polymeric nanoparticles derived from PLGA, are critical in design and assessment of innovative formulations in pre-clinical studies, leading to further early-phase evaluation to manufacturing of late clinical-phase drug products."

August Bioservices: Achieving Desired LNP Formulation Profiles

August Bio offers a full range of formulation development, analytical development, and cGMP manufacturing services, advancing clients' drug formulation needs from small-scale R&D through scale up to commercialization. The company is deeply rooted in sterile injectables, supporting formulations for injectable products in vials, bottles, prefilled syringes, cartridges, and IV bags that are liquid or lyophilized, aseptically processed or terminally sterilized. The company also has experience and capability in semi-solids, creams, gels, and ointments.

Mayurkumar Tamakuwala, Senior Manager, Formulations at August Bio, says one clear differentiator is August Bio's Lipid Nanoparticle (LNP) and Liposomal expertise. The company can work with a range of LNP formulation and sizing technologies to achieve the desired product profile. Capabilities for high-shear mixing, high-pressure homogenization, and microfluidization can be configured to develop robust, reproducible manufacturing processes in R&D studies and then scaled to GMP for both clinical and commercial applications. With analytical services ranging from dynamic light scattering for particle sizing, to LC/LC-MS/GC-FID/LC-CAD for lipid assays and residual solvent quantification, August Bio offers an end-to-end approach to product lifecycle development starting at LNP process development and product characterization, moving through clinical and eventually to commercial scale operations.

August Bio relies on proactive Design of Experiments (DoE) to predict and remediate challenges before a final formulation is selected. "If a customer comes to us with a formulation already in clinic, facing a set of CMC challenges, we use this same approach to optimize it and ensure continuity of clinical supply," explains Mr. Tamakuwala. "We differentiate ourselves from other providers of CDMO services on the basis of the expertise that our team brings to client projects to help resolve challenging obstacles and advance projects to successful completion."

Bionex Pharmaceuticals LLC: Setting Clients Up for Success

Bionex specializes in the formulation and development of novel topical, transdermal/transmucosal, implant, and nasal/inhalation drug delivery systems. Its CRMO services include pre-formulation, dosage form design, product innovation, product life-cycle management, integration with analytical chemistry, product stability study, clinical supply manufacturing, process development and optimization, IND-CMC package readiness and submission, and full support for quality system, technology transfer, regulatory and patent filings.

"Our mission is to realize the applications of biopharmaceutical and life sciences into commercial products and services that benefit human health," says Hock Tan, PhD, President, Bionex.

Most of Bionex's clients are virtual companies focused on early-stage development. "Maintaining our flexibility, agility, transparency, and cordiality, in many aspects such as dealing with changes in development timelines and budget, is our key factor in keeping our clients," he says.

"During the early stages of a program, you need a CMC partner that is responsive enough to incorporate the inevitable changes that accompany early-stage development, yet carry the resident expertise to skillfully perform the formal scientific testing required to validate your approach," says one Bionex client. "Bionex kept our program on schedule and set us up for future success."

Catalent: Embracing Time- & Money-Saving Manufacturing Capabilities

Catalent offers formulation, process and analytical development services, as well as clinical and commercial manufacturing capabilities across multiple modalities, including small molecules, biologics, and cell and gene therapies. The company's global network of facilities offers flexible and scalable solutions.

When it comes to manufacturing capabilities, William Wei Lim Chin, PhD, Manager, Global Scientific Affairs at Catalent, says that continuous manufacturing provides more efficiency because there is no downtime between batches. This leads to shorter production times and the potential to save money. In addition, the production process enables issues to be identified promptly, and steps taken to resolve these quickly, leading to a decrease in defects and more predictable product quality.

Twin screw extruder (TSE) technology is one such example that Catalent employs, and is used to produce amorphous solid dispersions that enhance the solubility and bioavailability of molecules with poor solubility. "This highly efficient mixing technology operates continuously and can be easily scaled, making it suitable for both R&D and commercial-scale use," he says. When integrated with other semi-continuous operations, it can provide an end-to-end process for manufacturing solid oral dosage forms.

Catalent, like many in the field of biologics manufacturing, is embracing the growing trend toward process intensification and continuous bioprocessing, as a means of improving production efficiency and productivity. One of the key elements within this is the use of single-use, disposable components, which play a critical role in enabling the seamless execution of continuous manufacturing workflows. Dr. Chin says: "For clients, the use of such technologies can reduce time to market, and mitigate against the risk of supply chain disruptions that may otherwise delay production."

CMC Pharmaceuticals: Holistic Approach to Development

CMC Pharma offers a range of formulation development services that include pre-formulation and formulation studies in addition to the preparation of formulation prototypes for *in vitro* and *in vivo* evaluation. CMC develops formulations that include tablets, capsules, and injectable solutions, as well as complex injectable formulations that include drug products with more than one active ingredient, long-acting formulations, suspensions, and dispersions.

"We utilize proven formulation approaches, scalable manufacturing processes, standard pharmaceutical container closures, and excipients that are found in FDA-approved products," explains Mike Radomsky, President of CMC. "We typically develop non-proprietary formulations, unless the customer is interested in developing intellectual property around their novel drug product. CMC has deep knowledge of pharmaceutical formulation science and can quickly execute studies to identify, prepare, and evaluate formulation prototypes. We can quickly and successfully develop a variety of formulations that have been tested in everything from rodents to non-human primates, and human clinical studies."

CMC Pharma takes a fully integrated approach to developing pharmaceutical

CMC scientists evaluate a variety of formulation approaches.

drug products, holistically considering preformulation, formulation, analytical chemistry, stability, and process development to ensure product development success. "Developing a product that cannot be produced at a commercial scale to meet commercial demands, has an insufficient shelf-life, does not have appropriate analytical methods available to ensure identification, purity, or potency, or utilizes excipients and formulation technology that are not found in approved products, can result in significant wasted development time, effort, and money," he says.

CMC Pharma recently helped a client with a drug product that had less than a three-month shelf-life. CMC scientists began by evaluating and understanding the degradation mechanism (e.g., oxidation, hydrolysis, light-mediated photo instability, etc.) and employing formulation stabilization strategies to minimize drug degradation to maximize shelf-life, Mr. Radomsky explains. CMC then quickly prepared formulation prototypes using these strategies and evaluated the stability profile of each prototype at stressed, accelerated, and long-term storage conditions. The end result was the identification of lead and backup formulations with a multi-year shelf life.

CycloLab: Excipients That Enable Innovative Drug Formulation

CycloLab Cyclodextrin Research & Development Laboratory Ltd. offers development of novel, often non-conventional, cyclodextrin-based formulation technologies. As a pioneer in the field, CycloLab relies on cutting-edge approaches of using cyclodextrins to solve various technical issues.

István Puskás, Formulation Scientist, CycloLab, describes how the company had been approached by a partner company to prepare an aqueous solution of an amphiphilic API that had the extreme tendency to self-aggregate. The API formed micelles and aggregates at very low concentration. "The goal was to formulate a clear, injectable solution to enable aseptic processing of the substance and subsequent filling into the final dosage container," he says.

CycloLab screened all suitable, parenterally acceptable cyclodextrins based on their solubilization property. "After selection of the best performing cyclodextrin, the ideal pH, and some non-conventional processing parameters, the right API/cyclodextrin ratio was optimized," says Dr. Puskás.

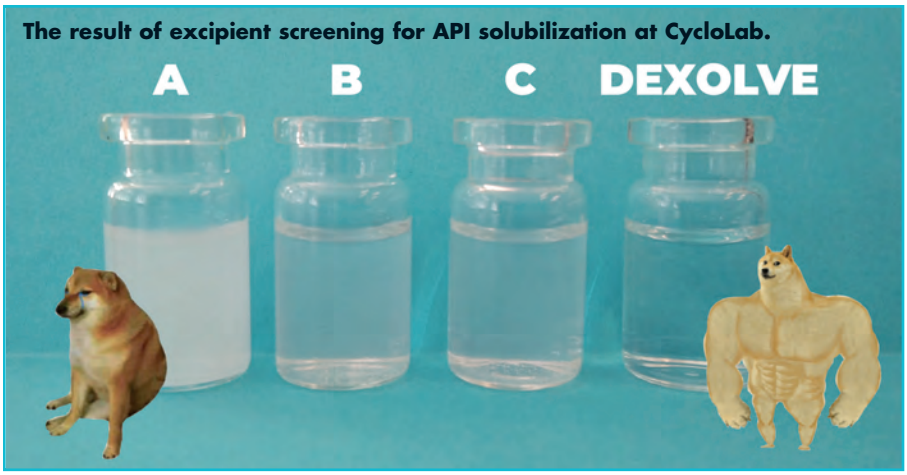
Due to the weak base type of the compound, betadex sulfobutyl ether sodium (Dexolve®) proved to be the most promising cyclodextrin for the preparation of the preformulation. The result of the development was a transparent, kinetically stabile solution of acceptable osmolality, characterized in a composition well below the safety threshold of human Dexolve exposure.

"The resulting liquid exactly matched the expectations of the customer," he says. The elaborated process was found novel, non-obvious, and easy to scale up to industrial use. Therefore the customer successfully obtained a granted patent for the process based on the cyclodextrin technology as a result of CycloLab's research."

Eurofins BioPharma Product Testing: One-Site Development Is Shortest Path to Commercialization

The Eurofins BioPharma Product Testing site in San Diego, CA, provides formulation and manufacturing services for the development of early phase and orphan drug products. Formulation services include pre-formulation, formulation design, and stress testing of sterile and non-sterile drug products. In the cleanrooms, compounding and sterile filtration are performed. A Cytiva Microcell for sterile filling and capping of vials needed to conduct clinical trials is used. Eurofins BioPharma Product Testing also manufactures GMP non-sterile products, excluding oral solids, in the cleanrooms.

"The manufacturing operator represents the greatest challenge to the sterility and particulate matter counts of an injectable drug product, yet the current norm in clinical manufacturing places the operator in the red zone, hovering over the filling and stoppering process," says Joe



The result of excipient screening for API solubilization at CycloLab.

Page, President of Eurofins BioPharma Product Testing's San Diego, CA, site.

Eurofins BioPharma Product Testing utilizes a robotic, gloveless, isolator, thereby eliminating the operator from the red zone. This disruptive manufacturing approach efficiently fills, caps, and stoppers the sterile vials in an ISO-5 isolator, resulting in a product with a higher level of sterility assurance, lower particulate matter, and reduced line loss. The Cytiva Microcell utilizes standard Type I vials and industry standard stoppers that are presterile and ready to fill.

"With a high level of digitization, the Microcell provides real-time data, such as isolator temperature, isolator humidity, isolator pressure, and hydrogen peroxide levels during decontamination and aeration," he explains. "The system performs many tests to ensure the integrity of the fill such as pressure leak tests and particle counting."

During filling, an on-board balance performs non-destructive weight checks to ensure the vials are filled with accurate amounts of drug product. Lastly, the viable environment is monitored with a TSB media that is controlled by the robot in the filling process.

The product testing robotic facility provides clients with a single site for sterile fill-finish, enabling all CMC requirements to be accomplished at one location. "It all starts with the analytical methods needed to measure a drug's potency and stability," Mr. Page explains. "From there, our scientists can design and optimize formulations leading to the production of clinical supplies. Additionally, we offer labeling, randomization, kitting, and distribution to clinical sites. While a drug product is in the clinic, Eurofins BioPharma Product Testing can monitor its stability in its labs. This one-site development translates into the shortest path for advancing your drug toward commercialization."

A recent formulation project involved developing a small-molecule immunosuppressant in an oral liquid dosage form. The project was challenged by the low solubility of the molecule in aqueous media. Using cyclodextrin to create inclusion complexes with the drug, Eurofins BioPharma Product Testing scientists screened different cyclodextrins, α, β, and γ to find the best form. Ultimately, the composition of β-cyclodextrin and the drug were optimized to achieve a 30-fold increase in concentration in a clinically presentable formulation.

Experic: Informed Ways to Work With Drug Sponsors

In discussions with potential clients, Experic gets asked: "How will we work together?" Justin Lacombe, PhD, Chief Scientific Officer at Experic, remarks that R&D organizations outside of the CDMO world tend to be very collaborative. Justin Lacombe, PhD, Chief Scientific Officer at Experic, remarks that R&D organizations outside of the CDMO world tend to be very collaborative. Data are constantly generated and discussed. Plans continuously shift to accommodate new insights drawn from new data sets and new analysis of data sets. Timelines are revised often. By contrast, when a CDMO contract

Eurofins scientist using Microcell Vial Filler for sterile fill/finish.

Experienced Experic staff working in the drum lab for a client.

is written, a specific piece of work is defined and contracted for, putting hard boundaries around what can be done. "So, how do we align R&D organization needs with CDMO business requirements?" he asks.

One key to this interaction is flexibility. From a process perspective, the CDMO should expect project requirements to change often. In most business processes, the changes identified by project management will trigger a change order. If the project is volatile, there can be many changes that happen day to day or week to week. "The business process should not overwhelm the client with individual changes, but seek to capture the changes without stopping the work," he says.

Flexibility does not end there. Information gained during experimentation can change the experiment's direction. He says: "Experimental plans rarely survive contact with reality. While there are good reasons to stay the course, the purpose of many R&D experiments is to obtain the most insight and information, not simply get a complete data set. This sometimes means diverging from the original plan."

Collaboration is also important. Experic staff has expertise in quality systems, regulatory filing, and analytical and formulation sciences. Dr. Lacombe says: "If we simply do the experiments we are told to, the project is not taking advantage of all we offer. Conversely, if our experts take the statement of work and simply come back with "answers," they are not taking advantage of the client's expertise and perspective. This is a team effort that can benefit the project from multiple perspectives." Collaboration may also involve consultants, other laboratories, device manufacturers, and other manufacturers. Working as a single team offers a greater likelihood of resolving issues.

Transparency and openness with clients and other team members are also important. Much like collaboration, transparency can lead to faster solutions. It does require a certain amount of trust between client and CDMO, he notes. "Because we are all human, mistakes will happen. If the focus is on liability (i.e., who pays for it), the likelihood of admitting fault decreases. That said, we will not charge a client to rectify a mistake we made. While there are some limits and give and take needed on this point, the important idea here is that we need to build trust."

A final important point is around the science and scientific process itself: While there is an art to some R&D, there is a lot of process. He concludes: "The more your thinking and project management is informed by methodical problem-solving methods, such as Quality by Design, Six Sigma, and Design Controls, the more efficiently you can reach a conclusion."

Hovione: Combining Experience With Technological Capabilities

Hovione is a CDMO helping to bring new and off-patent drugs to market via oral, inhalation, and nasal delivery. In oral drugs, where most new chemical entities suffer from poor bioavailability, Hovione has a comprehensive and accurate screening methodology for amorphous solid dispersions, ASD-HIPROS™.

"Amorphous solid dispersions are the leading formulation platform to address solubility limitations," says Filipe Gaspar, Vice President Technology Intensification at Hovione. "We complement this formulation expertise with extensive technological capabilities, including spray drying and hot melt extrusion. Spray drying is the fastest growing platform to overcome the solubility issues related to oral drugs. With the largest spray drying capacity worldwide, state-of-art scale-up science, and a very experienced team, we can help our customers bring new products to market in the most expedited manner."

The need to accelerate time to market is one of the reasons Hovione is investing in continuous manufacturing. Mr. Gaspar says continuous manufacturing is suited for all types of drug products for oral delivery, including the production of precision medicines and breakthrough therapies. "Its benefits over the traditional batch process are well known and include higher quality standards through continuous

monitoring of product quality, faster development times, and flexible supply chains," he says.

Adopting continuous manufacturing is challenging for all CDMOs, he adds, not only due to the additional technical complexity, but also because it requires quality systems that are aligned with a new paradigm.

"Obviously, we are not doing it alone," he says. "Crucial to this endeavor are important partnerships with leading technology providers, research institutions, and pharma companies that share our vision."

For instance, Hovione and Laxxon Medical recently entered a strategic collaboration to advance the use of 3D screen printing technologies for the pharmaceutical industry. The 3D technology displays numerous advantages, including the potential to produce unique or customized dosage forms with characteristics that cannot be achieved with conventional dosage forms and the ability to create tablets of any shape and size. It also allows for the option to easily adjust the number of active substances and individual components in the composition of the tablet and even to set the dosage individually for each patient for personalized medicines.

In the development and manufacture of pulmonary and nasal delivery products, Hovione has an end-to-end offering that includes formulation development, particle engineering technologies (spray drying, wet polishing and jet milling), precision capsule filling, and a range of dry powder inhalers.

Lifecore Biomedical: Beating the Timeline of a Complex Formulation

Lifecore Biomedical is a fully integrated CDMO with expertise in aseptic formulation, aseptic filling into syringes and vials, and final packaging of injectables. The company also produces premium, pharmaceutical-grade, non-animal-sourced sodium hyaluronate that is incorporated into most of the 25-plus commercial drug and medical device products the firm manufactures.

"Lifecore's extensive experience with complex projects enables us to help customers complete CMC activities quickly while offering the flexibility to be as hands-on as they need," says Ryan Swanson, PhD, Director of Process Development, Lifecore Biomedical. "For example, we recently collaborated with a three-person, virtual pharma team that required significant support to scale up their benchtop process to a Phase I GMP process within an aggressive timeline."

Within 10 months of receiving a signed SOW, Lifecore began manufacturing the first GMP batches for clinical studies – a significant achievement considering the investigative work and improvements needed to scale their processes, he explains. Beyond formulation process development, the project included numerous parallel activities, such as raw material sourcing, analytical test method development, supply chain management, regulatory support, and packaging.

The customer's formulation involves a polymer cross-linking reaction with various stages of filtration prior to final sterile filtration/filling. The reaction is time sensitive and concentration dependent, so the Lifecore engineering team performed a Design of Experiments (DoE) to gain insights on the reaction kinetics at scale and to understand the design space for producing acceptable product using the scaled-up process. In addition to the work around reaction kinetics, studies were performed to make improvements to mixing dynamics, hazardous gas containment, cleaning, and buffer preparation. "We sourced appropriate filtration components to produce quality product at scale and ensure sterility assurance," Dr. Swanson says. "We also had to qualify vendors who could provide chemicals appropriate for a Phase I GMP process."

Due to compressed timelines, the cus-

Lifecore Biomedical CDMO has proven experience with the challenging GMP formulation and filling of complex injectables.

tomer was not able to work within an 18-month lead time that was quoted for some equipment required to scale their process. With an extensive in-house inventory, Lifecore was able to utilize and adapt on-hand equipment to eliminate this problem.

During the 10-month, accelerated timeline, Lifecore produced a total of 10 (partial as well as full) batches to prepare for the first GMP batch. Dr. Swanson concludes: "We were able to align with our customer's timing requirements to get them to the clinic in their desired timeframe."

A Ligand scientist works in the lab to assess a client's formulation with Captisol.

Ligand Pharmaceuticals: Cyclodextrin Technology Proves Itself for Formulations From Ophthalmic to Nutraceutic

Ligand Pharmaceuticals offers formulation development services that focus on the use of a specifically modified cyclodextrin to enhance solubility, stability, and other formulation challenges. The scientists at Ligand have experience in developing many dosage forms, including parenteral, oral solid, oral solution, inhalation, ophthalmic, and nasal. Examples of formulation and analytical studies that Ligand offers include, but are not limited to, initial phase solubility studies, use of additives, application of various processing techniques, forced degradation, stability, and transfer to GMP CDMO facilities. Formulation development ranges from early development to clinical Phase III to commercial production and launch.

"Our capability to teach as well as practice our Captisol® (Sulfobutyl Ether Beta-Cyclodextrins) formulation technology is critical to the success of our clients' product development," says J.D. Pipkin, PhD, Vice President, New Product Development, Ligand.

Fifteen drug products have been FDA approved using Captisol for primarily parenterally administered products, and recently for the first oral product. And another six product approvals are expected over the next 18 months, including new routes of administration: topical ophthalmic eyedrop and subcutaneous patch infusion.

"This is a remarkable upswing in the adoption of the Captisol technology," says Dr. Pipkin. "Most have been collaborative development efforts, including initial technical feasibility assessment, formulation development, and preclinical proof-of-concept studies. This has evolved to stage-appropriate regulatory support and participation in pIND and pNDA meetings and providing submission sections and responding to review questions."

Ligand recently helped a partner to overcome stability issues of an API so that it could be spray-dried for an inhaled dosage form preclinical efficacy assessment. "This was a very challenging project because degradation of the API affected both the analytical method and the formulation," explains Lian Rajewski, PhD, Senior Research Investigator at Ligand.

Captisol was also incorporated into the analytical method to obtain reproducible results. Processing techniques were key to formulating the drug solution to allow spray drying to occur. The client was able to obtain the desired solid particle size for the final spray dried formulation and use multiple formulations in non-clinical studies.

In another example, phase solubility studies were performed with an API to be used in a concentrated subcutaneous dosage form. The formulation challenge was to overcome the limited solubility of the API. pH jump processing techniques were used to prepare a formulation in a biocompatible-acceptable pH range with the desired stability. Buffer choice and ionic interactions were an integral aspect of the final formulation.

Additionally, several nutraceutical or natural product projects have been tackled recently by Ligand. In one project, the multiple active constituents were enriched using thermal processing of the raw material with Captisol, resulting in improved

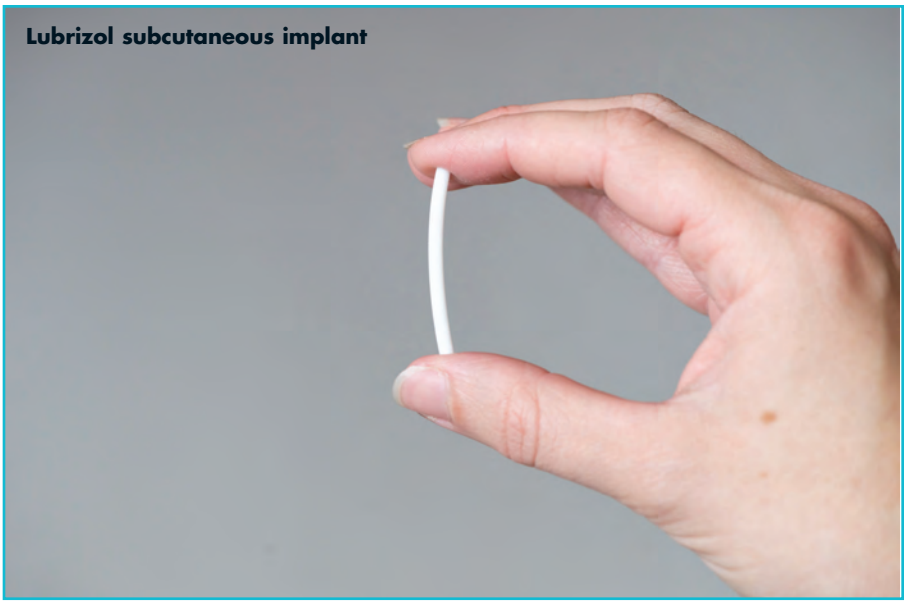
bioavailability. In the other project, the challenge was to use Captisol to solubilize and stabilize a natural product to prepare a palatable oral solution. Again, thermal jump and dispersion/levigation processing techniques were the key to attaining the highest concentration of the actives in final solution, says Dr. Rajewski.

Lubrizol Life Science Health: Develops Implants, Injectables, & Topicals

Lubrizol Life Science (LLS) Health supports clients from concept through commercial manufacturing with a focus on high-value, low-volume, more complex formulations – as well as a project somewhere within and between those two phases of a product development cycle. The company's core offerings include: development of long-acting drug products for various routes of administration (i.e., implants, injectable depots, and vaginal rings); solubility and bioavailability enhancement (i.e., nanomilling and solubility-enhancing excipients); and aseptic processing for both clinical and commercial drug products.

"We are an ideal partner for clients focused on ophthalmic drug delivery because we have the resources to develop implants, injectables, and topicals, and can provide aseptic manufacturing for some of these dosage forms," says Jite Okoh, Director, Drug Eluting Device Development, LLS Health. "For certain drug-eluting devices, we have the capability to not only manage development and clinical material, but we can also bring these into commercial manufacturing."

As an example, LLS Health served a client that produces a commercially available biodurable drug-eluting device for long-acting topical delivery. Due to its design and material of construct, this device requires significant manual assembling, resulting in high manufacturing costs. After evaluating risks, costs, and optimization options, LLS Health recommended and identified an appropriate change in the materials of construct.


Lubrizol subcutaneous implant

"Utilizing our knowledge of thermoplastic polyurethane (TPU) chemistries and their impact on drug delivery, we redesigned the drug device product using our Pathway™ TPUs," says Mr. Okoh. "We maintained the properties of the existing commercial product while streamlining the manufacturing process, hence significantly reducing manufacturing costs."

He adds that LLS Health differentiates itself with onsite technical expertise. We can handle and formulate numerous pharmaceutical actives (APIs), covering various therapeutic indications, including highly potent compounds. "We hold two DEA licenses – one for manufacturing and one for analytical," he says. "We are able to work on all schedules for preclinical and clinical development, depending on the drug products. These abilities and licensing empower us to work with a significant range of APIs, allowing us to successfully develop products and take our clients to GMP production."

LLS Health has developed continuous manufacturing processes for several of its formulating techniques, including hot-melt extrusion and its continuous cryomilling process. He says: "We've implemented phase-appropriate technologies and methodologies to help reduce our clients' costs and timelines to progress them through the various development phases as quickly as possible. Our organization has also introduced feasibility programs to quickly help clients confirm proof-of-concept at a reduced cost and timeline for many techniques, including nanomilling, formulating microspheres, and drug-eluting products for long-acting drug delivery."

In addition to onsite expertise and manufacturing processes, LLS Health offers customers a one-stop-shop for product development, which leverages Lubrizol's polymer chemistry expertise that has been shown to significantly accelerate the development and timelines of drug-device products, says Mr. Okoh. "Our organization-wide cooperation and collaboration provide value to clients throughout their projects' lifecycles. In some cases, clients approach us with the desire to develop strategic partnerships. We can execute multiple programs with

Scientist Sydney Marchando fabricating lipid nanoparticles using Particle Works' ANP Microfluidic System in the Phosphorex facility in Hopkinton, MA.

our partners and take projects from concept to commercialization for several dosage forms. Our holistic in-house approach reduces risk while producing a product that matches our clients' desired target product profile."

Phosphorex: Tailored Technological Approaches

As a CDMO, Phosphorex is a leader in the formulation, process development, and manufacturing of particle-based formulations, including polymeric microspheres (PMS), lipid nanoparticles (LNP), and polymeric nanoparticles (PNP). For the past 17 years, the company has developed therapeutics in the application areas of long-acting injectable, tissue-targeting, and delivery of nucleic acids for more than 100 pharma and biotech companies. Phosphorex has established a variety of particle-forming modalities that can be tailored to the need of specific projects or applications, including rotor-stator homogenization, high-pressure homogenization, in-line homogenization, nanoprecipitation, micro fluidization, and T-junction mixing. Phosphorex has also partnered with leading technology providers to offer state-of-the-art microfluidic equipment and systems in its facility.

Bin Wu, PhD, Founder, President, and Chief Scientific Officer of Phosphorex, relates that the COVID pandemic triggered new trends in pharmaceutical development, opening the gate to new nanotechnology-based programs across various therapeutic indication, such as immunology, immune-oncology, RNAI, cell therapy, and vaccines. Phorphorex has adapted robust batch and semi-continuous processes dedicated to LNP development with the goal of reducing the batch size and making the most efficient use of the RNA payloads, explains Dr. Wu.

Working to benefit clients, Dr. Wu describes the situation of a client with a daily injectable peptide seeking to develop an extended-release formulation that would enhance efficacy, improve patient compliance, and extend patient life. "Up until then, no other CDMO had been able to help," Dr. Wu says. "Within three months, Phosphorex was able to develop a microsphere formulation that increased peptide loading by 35%, encapsulation efficiency by 87%, with a burst release of less than 5%. The formulation demonstrated sustained release in rodents and NHPs. Phosphorex further optimized and up-scaled prototype formulation and process, produced tox, preclinical batches for IND-enabling studies, and successfully transferred a developed process to a partner GMP site for the manufacturing of the clinical batch."

Scorpius BioManufacturing: Outsourcing Clinical Manufacturing Requires a True Partnership

Scorpius BioManufacturing is boutique CDMO with integrated solutions for large-molecule cGMP manufacturing, process and analytical method development, product characterization, and release testing needs. Scorpius' San Antonio, TX, facility currently has capacity for both mammalian and microbial clinical manufacturing projects, which is well-suited for collaboration with emerging biotechs, academic labs, and research facilities, and large pharmaceutical companies, says Steve Lavezoli, Vice President of Business Development, Scorpius BioManufacturing.

"Flexibility is the name of the game in accelerating biomanufacturing development timelines," he says. "However, the current capacity crunch often results in frustration among sponsors when they feel CDMOs are not flexible or attentive enough. There isn't an incentive for CDMOs to be flexible when demand for manufacturing continues to outpace supply. Large CDMOs have the luxury of choosing only the highest volume programs with the best ROI. This means frustration is especially high among small biotechs and programs coming from aca-

demic labs – time and time again these innovators pour their life's work into R&D only to find out CDMOs put them at the back of the line. If they are fortunate enough to get a spot in line, they'll often feel like the CDMO dictates the terms and tone, creating an inflexible partnership."

His advice is for drug sponsors to look for basic facility design and business best practices when selecting a CDMO to ensure flexibility is part of the partnership from the outset. CDMOs with single-use systems, modular clean rooms, and on-site process development and analytical services are examples of how flexibility can accelerate development timelines.

Additionally, being an entirely single-use facility allows faster cleanroom changeover while minimizing risk. "Single-use systems can save weeks of cleaning and release time, and this speed ultimately benefits client programs," he says.

Having single-use technology in modular cleanrooms is another plus. While ballroom designs might seem appealing in terms of maximizing space, the flexibility offered by a modular facility ultimately means increased speed along with a decreased risk of contamination, he adds. Finally, having on-site process development and analytical services can save time and help clients quickly pivot when needed.

Flexibility goes hand-in-hand with responsiveness. Clients should expect a high level of responsiveness from the RFP stage all the way through product release, he advises. "Responsiveness isn't just required from a CDMO's program management and business development team – clients should expect to have open lines of communication with subject matter experts in quality, operations, and leadership levels as well," he continues. "Building relationships with cross-functional teams at CDMOs means clients can have discussions about things like strategic financing models, process optimization, and timeline transparency."

Tergus: De-Risking Development of Topical Drugs

Tergus is a full-service CDMO specializing in dermatology product development and commercial manufacturing. End-to-end formulation development and manufacturing services starts with molecule screening for topicalability, formulation development, and analytical testing/stability and ends with *in vitro* testing, including *in vitro* release test (IVRT) and *in vitro* permeation testing (IVPT).

"Our front-end capabilities enable us to de-risk the development of topical drug products by verifying that the molecules have target engagement, while our IVRT and IVPT services on the back end ensure that the formulation developed is effective at releasing the molecule into the skin tissue," says Dr. Vijendra Nalamothu, Executive Chairman & CSO of Tergus.

During the manufacturing stage, Tergus adheres to Quality by Design (QbD) principles to de-risk early scale-up and commercialization issues. In addition, all of Tergus' manufacturing equipment is produced by the same manufacturer to reduce surprises and scale-up quickly and efficiently.

To quickly scale biopharma customers' manufacturing batches from small to large scale, Tergus has implemented a 'bracketing' strategy for both manufacturing and fill stages. The bracketing strategy, in combination with its equipment that uses the same rotor/stator homogenization principles across the entire equipment line, enables Tergus to scale rapidly and efficiently from 10 to 1,500 liters.

A biopharma customer recently asked Tergus to develop a unique topical formulation that could withstand the suspendability of a drug substance embedded in a synthetic polymer matrix. "The weight of this drug-polymer combo was difficult to maintain in a conventional suspended gel vehicle, so Tergus' team of topical experts developed a formulation comprised of novel, approved excipients and structure-forming waxes," explains Dr. Nalamothu. "Our new, innovative formulation stabilized the suspension and enabled it to permeate into the skin."

During manufacturing process development, Tergus identifies all the critical process parameters (CPPs) and addresses them using critical quality attributes (CQAs). Once the process is fully robust and reproduceable, the ability to move from one batch size to another is much faster and requires less regulatory scrutiny. Similarly, Tergus' packaging process follows the bracketing strategy for the lowest and highest fill weights. This approach allows customers to choose any packaging size between the lowest and highest fill weights without requiring additional stability studies.

Dr. Nalamothu says that Tergus is continually evaluating new, innovative technologies to optimize formulation development and manufacturing services. The company is currently evaluating 3D printing of the skin for its *in vitro* permeation studies, as well as statistical design of experiments (DoE) tools and QbD software programs for its manufacturing division. And, Tergus recently implemented a state-of-the-art track-and-trace serialization solution in its manufacturing division.

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DEVICE DEVELOPMENT

How to Ensure pMDI Drug Products Are Fit for the Future Market Landscape

By: Ross Errington

INTRODUCTION

Demand for pressurized metered dose inhalers (pMDIs) continues to grow, driven by increases in the prevalence of serious chronic respiratory diseases across the globe. pMDIs offer a number of performance and useability advantages that make them ideal for therapies treating these conditions.

However, the market landscape is changing fast, particularly when it comes to the regulatory environment governing medical devices and the propellants used in pMDIs. There have been stringent revisions to the EU Medical Device Regulation affecting the classification of components that may be used in pMDIs device developers and manufacturers need to be aware of.

The Kigali Amendment to the Montreal Protocol - an international agreement to gradually reduce the consumption and production of hydrofluorocarbons (HFCs) to reduce global warming - also impacts the pMDI market. This is due to the device's current use of HFCs as a propellant. The Amendment has led to significant legislative updates in major pMDI markets, including the US, EU, and UK, with the potential to affect future pMDI usage.

Efforts to meet the targets of the Kigali Amendment are being complicated by new proposals to update the EU's Registration, Evaluation, Authorization, and Restriction of Chemicals (REACH) regulation. The proposed changes will restrict the manufacturing and use of polyfluorinated alkyl substances (PFAS) - there is concern this will impact the use of alternative low-GWP F-gases that could help the pharmaceutical industry transition away from HFC propellants. The proposals also have the potential to restrict the usage of coatings typically used in the container closure system for some pMDI products.

With all of this in mind, pharmaceutical companies need to carefully consider both the design of their pMDI devices and their manufacturing processes to ensure they continue to be compliant with a diverse range of fast-changing regulations. How can pharmaceutical companies ensure their pMDI products are fit for the future?

A FAST-GROWING MARKET

The pulmonary or respiratory drug delivery market was valued at $57.4 billion in 2022 and is expected to reach $76.9 billion by 2027.[1] pMDIs account for a large proportion of this increase - the market for pMDIs alone is anticipated to be worth more than $22 billion by 2031, up from $16 billion in 2022, with a CAGR of 3.1% throughout the forecast period.[2]

An increase in diagnoses around the world of chronic pulmonary conditions, such as asthma and chronic obstructive pulmonary disorder (COPD), is one of the key drivers behind this ongoing market expansion. In 2019, COPD killed 3.22 million people globally, and the number of deaths rose by 17.5% between 2007 and 2017.[3,4] COPD affects 1 in 10 of the adult population and is one of the three most common causes of death worldwide.[5] Asthma, meanwhile, affected an estimated 262 million people in 2019 and caused 455,000 deaths.[6]

Unique features of pMDIs make them particularly suitable for use in combination products to treat these conditions. They are efficient to manufacture, meaning they are cost-effective to provide to patients living with chronic conditions. They offer

unique breath-independent actuation, reducing the inspiratory flow rates needed to achieve adequate drug deposition in the lung.[7] This makes them ideal for treating both elderly people and children, providing HCPs with confidence the patient is receiving a uniform drug dose every time.

With this in mind, it is no surprise there is such a clear correlation between global prevalence of chronic pulmonary diseases, and increases in demand for pMDIs.

A REGULATORY ENVIRONMENT IN FLUX

There are three key updates that pharmaceutical companies need to be aware of:

- **Impacts of the EU Medical Device Regulation (MDR):** The MDR has been established to replace the Medical Device Directive (MDD) and the Active Implantable Medical Device Directive (AIMDD), two separate directives governing the design of all devices used for medical purposes, including inhalation device technology. Under the provisions of the MDR, all new and existing devices (undergoing a significant change) used with medicinal products (combination products, such as pMDIs) must show conformity to the general safety and performance requirements (GSPRs) or Annex I of the MDR. In February 2023, the MDR transition periods were extended, meaning there will be a delay in MDR implementation for specific classifications.

- **Changes in propellant regulations in key markets following the signing of the United Nations (UN) Kigali Amendment:** In 2016, UN member states signed the Kigali Amendment to the Montreal Protocol, which aims to phase down global consumption of hydrofluorocarbons (HFCs) by 80%-85% by 2047.[8] HFCs are widely used across many industries, including the pharma sector, as propellants - and they have been the principal propellants in pMDIs for decades. However, the most widely used HFCs have been shown to have an impact on global warming due to their high Global Warming Potential (GWP) and long atmospheric life (AL). As a result of the Amendment, new legislation has been enacted in key pMDI markets, including the EU, UK, and the US, and in some cases is being updated in order to accelerate the phasedown. At the time of writing, it is unclear what the revised timelines will be for phasing down the use of these gases in pMDIs in all key markets. Nevertheless, it is important to begin the transition to low-GWP propellants now to ensure ongoing compliance when the timelines are confirmed.

- **Joint restriction proposal submitted under the European REACH regulations for PFAs:** Submitted in January 2023 by the national authorities of Germany, the Netherlands, Norway, Sweden, and Denmark – this calls for further restrictions or even bans on HFCs and hydrofluoroolefins (HFOs).[9] This includes any CF2 group or a CF3 group substance, such as HFC and HFO propellants and refrigerants. The restrictions would potentially include gases, such as 1,3,3,3-Tetrafluoropropene [HFO-1234ze(E)], which are being explored as low-GWP alternatives for current pMDI propellants. Any restrictions on their manufacture and use would have negative implications for the industry's efforts to continue to supply effective inhalation drug products, while working toward meeting

global regulations phasing down HFC use. While this is just a proposal at the time of writing, if it does pass, and the ban is enforced from 2025, then the industry would have just 18 months from that date to remove any pMDIs containing these gases from the EU market.

FACTORS TO CONSIDER DURING DEVELOPMENT

To prepare for the future and ensure continued compliance, pharmaceutical companies will have to consider a number of design, formulation, manufacturing, quality control, and regulatory factors.

Device & Formulation Design Requirements

The Kigali Amendment has particularly significant ramifications for the design of the container closure system of pMDI devices and the formulations administered by them, due to the need to explore alternative propellants that are more sustainable. To date, a number of potential alternatives to the current propellants used in pMDIs are being evaluated - not just HFO-1234ze(E), but also 1,1-difluoroethane (HFA-152a). However, the selection process for new propellants is complex and several aspects need to be considered:

- **Safety & impact on the environment:** The safety of the new propellant in isolation needs to be investigated, in addition to its safety when combined with the pMDI container closure system and the medicines being delivered. This dual focus has always been a challenge when formulating combination products. However, the addition of relatively unknown propellants further complicates the process. It is also important to consider low toxicity. It is of course vital that any propellant is safe for human ingestion and there is no detrimental impact/interaction with drugs. Flammability of the propellant is also an issue that needs to be considered, and ATEX certification of the production line machinery will need to be addressed if there is any explosive risk.

- **Compatibility with device & formulation:** Any new propellant must be compatible with pMDI container closure systems such as cans and valves as well as the actives and other ingredients within the drug formulation. Compatibility between the new propellants and container closure systems can be ensured by maintaining seal integrity and valve delivery performance through the product shelf-life. Acceptable levels of leachables and extractables are also key, making comprehensive testing essential. Propellant vapor pressure and molecular weight also need to be considered when determining the propellant leak rate. This can be evaluated by exposing the filled canisters to extreme temperatures and pressures and then testing them at different points in time. However, ahead of this process, it is possible to use calculations to accurately predict propellant leakage rate, as well as establish the root cause of any deviation from the acceptance criteria.

- **Physical & chemical properties of the propellant:** The physical and chemical properties of the propellants are important when formulating medicines into pMDIs. Two of the leading propellants being explored have similar properties to currently used HFCs in terms of vapor

pressure, density, and compatibility with surfactants and solvents such as ethanol. This suggests radical changes to formulation platforms may not be required, but appropriate studies are needed to confirm this.

- **Scalability concerns:** The ability to scale up manufacturing processes for devices and formulations using any new propellant is an important consideration. Failure to take this into account at the design stage could lead to costly delays in commercialization, whether for new treatments or for reformulation of existing pMDI treatments.

Regulatory Issues to be Factored Into Future Commercialization Processes

Changes to the design of their pMDI devices and formulations in response to the new legislation being introduced in key markets as a result of the Kigali Amendment are not the only measures pharmaceutical companies will have to take to prepare their pMDI drug products for the future. They will also have to factor in changes in the way they manage regulatory approvals and quality control processes for new or updated devices to meet the requirements of new device regulations around the world. In particular, to ensure compliance with the MDR in the EU, they will have to think about the following:

- **Quality management system (QMS) changes:** Under the new MDR, pharmaceutical companies will have to update their design control and Good Manufacturing Practice (GMP) protocols. They will have to include new clinical evaluation procedures, enhancing the collection of clinical data. A Post-Market Surveillance (PMS) system will also need to be in place to monitor the real-world performance of the pMDI after commercialization.

- **Supervision of notified bodies:** The MDR has expanded requirements concerning the designation of notified bodies. Developers must find a notified body to review information regarding the general safety and performance requirements (GSPRs) under Annex 1 of the MDR in order to issue an opinion that the product conforms with the requirements. This will need to be considered at the development stage for any new drug development project, or device re-design to ensure the regulatory filing process moves as smoothly as possible.

EXPERT SUPPORT IS VITAL

The market for pMDIs is changing rapidly. Pharmaceutical companies need to take action now if they want to continue to benefit from the unique convenience and manufacturability benefits of pMDIs.

The prospect of having to update not just the design of devices and formulations, but the regulatory and commercialization processes can be daunting for many companies. However, with the right expert support, they can be confident they have the tools they need to continue to meet stringent requirements.

Contract development and manufacturing organizations (CDMOs) that specialise in pMDI development have the experience and in-depth design and regulatory knowledge to help. With their assistance, pharmaceutical companies can keep their pMDI products up to date with the latest market and legislative changes so they can continue to provide the best possible treatments for patients living with chronic pulmonary diseases. ◆

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BIOGRAPHY

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Lifecore Biomedical

Lifecore Biomedical: Emerging From Under the Radar

After more than 2 decades in pharma with a focus on the CDMO space for the prior 15 years, Darren Hieber was contacted about a new position at Lifecore Biomedical. While Lifecore had not been on his radar, he was intrigued to learn more. He soon discovered that, with expertise in highly viscous injectables and a strong foundation in ophthalmics, Lifecore had developed a formidable reputation in a niche area of the parenteral market.

Now, he is leading the charge to find opportunities for Lifecore to apply the company's expertise to a broader range of programs. *Drug Development & Delivery* recently interviewed him about progress after his first year as Sr. Vice President of Corporate Development and Partnerships.

Q: You have bit more than a year under your belt at Lifecore. What motivated you to join their team?

A: Years ago, I joined a mid-sized CDMO that was later acquired by a much larger organization. Over time, I missed the smaller culture in which I had felt more connected to customers and their projects. Joining Lifecore felt like a return to the earlier days of my career, and I knew I would be able to lean on my broader experience to make an impact.

It also offered me an opportunity to build a commercial team aimed at growth. CDMO growth translates to more customers served, increased availability of therapeutic options, and greater impact on patients. It is personally gratifying to be part of growing a business that contributes to the well-being of others.

Q: Beyond the level of involvement with customers, what attracted you to Lifecore?

A: I was impressed by the depth of in-house competency and experience. Lifecore's legacy since the 1980s was in manufacturing hyaluronic acid (HA), which is extremely viscous. Driven by customer need, the company undertook aseptic formulation and aseptic filling of injectable drug and medical device products using HA – in excess of 100,000 cP. Over decades, the

company evolved into an end-to-end CDMO with proven process development knowledge spanning from early phase and clinical trials to aseptic fill/finish of vials and syringes.

What stuck with me was the unique capability to undertake complex formulations. When you can handle molecules with the toughest characteristics, it demonstrates the differentiation in capabilities that allow Lifecore to be a valued development partner for a broad spectrum of new therapies. And Lifecore was already proving that through successful process development projects in different therapeutic categories.

Q: So, it sounds like there has been a great deal of expansion in capabilities over time. Why do you believe Lifecore remained under your radar as a contract manufacturer?

A: The first reason is customer longevity and focus. I mentioned that we have been working alongside a base of customers in ophthalmics for decades, developing solutions to fulfill their emerging requirements. As you can imagine, the global regulations for treatments that will be used during eye surgery are extremely stringent, so the robustness of our processes had to be proven. For a considerable number of years, we were dedicated to servicing this core base of customers and getting deeper with their novel therapies. Lifecore had been growing organically via word of mouth and reputation, and while that is positive, it only takes you so far.

I believe another reason Lifecore is not as well-known as other CDMOs is related to our culture. The people at Lifecore, including the leaders, are hard-working and unassuming. They have a strong desire to solve challenging problems for clients utilizing expertise within the building; they have not been as concerned about promoting themselves outside the walls of Lifecore. A recent prospect visited our campus and commented that Lifecore operates with a "quiet confidence."

Q: It sounds like Lifecore developed a lot working with their first partners. What were the important takeaways?

A: Our business was built on deep partnerships. We had a major stake in the success of our partners' products because we were investing in the facilities and capacity to develop and manufacture those products. More than 40 years later, our leaders remain approachable and involved with our partners so we can continue to evolve with them. With substantial capex and infrastructure lead times, it is essential to understand our partners' next steps and plan with the capacity to serve them.

One of the other main benefits was the strength of our cGMP operations. Our Quality Management System, compliance group, and our facilities had to grow to serve the needs of partners. Because it was needed by our partners, our QMS covers API and excipient, medical devices, biologics, and drug and combination products. As their patient base expanded globally, we sought additional international certifications. As demand for analytical testing increased, we expanded our on-site services to the point at which we now handle almost everything in-house. This has enabled the expansion and diversification of our current capabilities and put us in position to manufacture the more than 25 commercial products we make today.

Q: Let's shift gears a bit. With a title calling out corporate development and partnerships, it appears Lifecore brought you on board to increase awareness and opportunities. How are you doing that?

A: Lifecore has a great story to tell, and I have been collaborating with our team to get out there and share it. We are capturing what it means to work with Lifecore and articulating that to others. Our message to potential partners is YOU Define the Starting Line, which means we will meet them where they are in any stage of their project. We work with everyone from virtual pharma to long-established companies, offering the flexibility to be as hands-on as they want or need. We also provide services from early clinical through to ongoing commercial supply.

Q: What do you believe is next for Lifecore?

A: Building on our foundation, Lifecore has the potential to translate expertise across a broader spectrum of pharma and biotech companies. With an increased need for parenteral products along with growing demand for outsourced manufacturing, the momentum is already building. With additional isolator-based filling lines becoming operational in the coming year, Lifecore will be offering increased capacity to serve existing and new partners.

Another factor helping us meet demand is our location in Minnesota, which has available space for physical expansion as well as a strong, experienced labor force. Also known as Medical Alley, Minnesota is the number one healthtech cluster in the world. According to the Medical Alley Association, which Lifecore Biomedical supports, the concentration of bioengineers and biomedical engineers within a 60-minute commute of Minneapolis is four times more concentrated than the national average.◆

EXCIPIENT TECHNOLOGY

A Juggling Act: Factors at Play in Your Choice of Solubilizing Parenteral Excipients

By: Joey Glassco, MBA

INTRODUCTION

It is a well-known fact the oral drug delivery route is preferred to any injectable route by the majority of patients. However, parenteral delivery, which includes intramuscular, subcutaneous, and intravenous administration, is invaluable for a variety of compelling reasons. Chief among these is the ability of injectable drugs to bypass gastrointestinal first-pass metabolism, which greatly reduces the concentration of an administered drug and its bioavailability.

Not all injectable formulations have equal requirements, however, and particle size is a key consideration that must be taken into account. For intramuscular and subcutaneous administration, API particle size can be larger, but for intravenous delivery, particles must be on the nanoscale. In addition, some APIs can also be cytotoxic and irritating to tissue, ruling out the oral or subcutaneous routes and necessitating intravenous administration.

Adding to the complexity, as in other routes of administration, poor water solubility can be a challenge for injectable drugs that must be addressed. A trend for new drug candidates with poor aqueous solubility exacerbates the issue. At present, 60% to 90% of potential new APIs in development pipelines, and more than 40% of those on the market, are poorly water soluble.[1]

Insolubility issues can effectively prevent life-changing parenteral drugs from achieving the necessary bioavailability for the desired therapeutic effect, causing them to fail in clinical trials. With the price tag on bringing a new drug to market amounting to approximately $1 billion, candidate failure during clinical trials due to poor solubility can have harsh financial consequences.[2] Most importantly, patients can ill afford otherwise viable drugs being discounted due to low solubility, especially in light of the fight to develop cures for cancers and orphan diseases.

Taken together, these factors have led to a strong drive for effective, non-toxic solutions to poor drug solubility. Finding options that can provide adequate drug loading can be a challenge.

EXCIPIENT-BASED METHODS TO COMBAT POOR SOLUBILITY

There are a number of methods for enhancing the solubility of parenteral drugs, and each comes with its own advantages and disadvantages.

Tweens are ubiquitous in the pharmaceutical industry as solubilizing excipients. Referring to polysorbates, most commonly polysorbate 20 and polysorbate 80, these long chain molecules have both hydrophilic and hydrophobic segments that allow them to emulsify poorly water-soluble chemicals. While effective in many situations, they can suffer from instability and are known to give rise to hypotensive effects in dogs – a drop in blood pressure that can induce fainting.[3]

Cyclodextrins have been effectively associated with neutral, anionic, and cationic APIs to enhance their solubility. They can be utilized for both lyophilized or solution formulations. However, as the molecules work by complexing APIs in a hydrophobic pocket, it is not applicable across the board and is limited to APIs with the ideal shape, size, and charge. With an inclusion ratio of 1:100 (API:solubilizer), cyclodextrins give rise to low drug loading compared to other options, making it potentially difficult to achieve the maximum tolerated dose of the API.

Polyethylene glycols (PEGs) are another traditional excipient used to enhance the solubility of drugs. Containing both polar and non-polar groups, PEGs are soluble in a wide variety of solvents, including water, and when included in a drug formulation, can effectively enhance aqueous solubility. However, potential toxicity concerns and adverse side effects related to the use of PEG are driving the industry to seek out alternative means of enhancing solubility.[4]

Apisolex™ polymer, composed of building blocks occurring or produced through natural processes in the body, has emerged as a non-toxic, non-immunogenic, and biocompatible alternative to PEG that can rise to the challenge of poor solubility. The technology leverages an amphiphilic multi-block copolymer. This incorporates a hydrophilic poly(sarcosine) block and a second drug-encapsulating block composed of a mixture of hydrophobic D- and L- poly (amino acids). Unlike organic co-solvents and surfactants, Apisolex polymer is a benign ingredient that doesn't add toxicity to the drug vehicle. It works through a highly flexible nanoencapsulation method, which allows it to be universally applicable to APIs as a solubilizer and to outperform alternatives.

THE MECHANISM OF NANOENCAPSULATION

Apisolex technology works by forming nanomicelles around API molecules. The insoluble API, either crystalline or amorphous, and Apisolex polymer are solubilized and then mixed in an aqueous media. Operating on the principle that "like attracts like," the hydrophobic ends of the Apisolex polymer cluster around the hydrophobic API. Meanwhile, the hydrophilic ends point outward, creating soluble nanomicelles. The solution can be sterile filtered or autoclaved depending on the physical and chemical stability of the API.

These micellular structures that encapsulate the API form as the solvent is removed from the solution or emulsion during diafiltration and/or lyophilization. If lyophilized, the drug product reconstitutes in saline in less than 30 seconds, ready for administration.

This mechanism of action allows Apisolex excipient to be more universally applicable to APIs, offering the flexibility to accommodate molecules of wide-ranging shapes and sizes. As nanomicelles form on the nanoscale with Apisolex technology, it can produce soluble drug particles in the appropriate size range for intravenous administration, while offering the flexibility to create larger particles for the subcutaneous and intramuscular routes. It also enables rapid evaluation, facilitating a shorter development cycle for clinical formulations. Apisolex polymer's highly effective performance has been shown to enhance solubility by up to 50,000-fold.

THE IMPORTANCE OF SCALE

While innovative technologies are key to solving the challenge presented by poor solubility, in order to be practicable, they must also be scalable. Complex manufacturing techniques can cause complications during scale up. As such, allowing developers to stick with simpler techniques they are familiar with gives more confidence when it comes to scaling up production. For example, injectable-grade Apisolex polymer is compatible with standard, scalable formulation techniques, such as solution mixing or oil-in-water emulsion formulation, with more than 90% API re-

covery. This can help to streamline development and reduce API waste, helping life-changing drugs reach patients in need faster.

TAKING A LONG-TERM VIEW: IP PROTECTION

Intellectual property (IP) protection is an invaluable resource to protect future success when developing a new drug formulation or adapting an existing one. Incorporating a novel excipient with robust patent protection can assist with securing IP protection. For instance, with a long patent life remaining, Apisolex technology enables both the formulation of new chemical entities and the reformulation of existing APIs to enhance their therapeutic effect and deliver improved patient outcomes via the FDA's 505(b)(2) regulatory pathway. By breathing new life into APIs that failed to progress due to solubility issues – while also ensuring patent protection – novel technologies such as Apisolex excipient open up new avenues for pharma companies to deliver important drugs to the market.

PUTTING APISOLEX TECHNOLOGY TO THE TEST

Scalability, safety, and IP protection are all important concerns. But ultimately, if performance is lacking, it will be necessary to seek out a different approach to improve solubility. This is a crucial factor in your choice of excipient. The solubilization properties of Apisolex polymer were examined in comparison with other excipients for a series of poorly water-soluble APIs. The experiments were conducted by non-optimized, standard dispersion techniques (mixing or homogenization), followed by dilution or lyophilization and reconstitution with a goal of simply evaluating the comparative performance of the various excipients. Toward that end, relatively low success metrics were selected:

- A target API concentration of 500 μg/ml after dilution or reconstitution
- Turbidity (NMT 100 NTU)
- Particle diameter (NMT 150 nm)
- Drug recovery after filtration (NLT 80%)

These metrics, if met, would result in end-product solutions that would be clear, homogeneous, or at worst, slightly turbid.

Series A compared Apisolex technology to the tweens, polysorbate 20, polysorbate 80, and Cermophor® for a variety of poorly water-soluble APIs. Only Apisolex polymer worked across the board, successfully solubilizing every API, and it did so at an API to solubilizer ratio much higher than that of traditional excipients.

Similar results were found when Apisolex excipient was tested against PEG-PLGA, TPGS and Captisol®. The universal applicability of Apisolex technology relative to other techniques with this series of APIs was again demonstrated in comparison with other solubilizers processed using the same lyophilization and reconstitution technique.

In additional experiments conducted for the experimental APIs, Apisolex excipient increased drug solubility by up to 50,000-fold.

The safety and toxicity of the Apisolex excipient was also evaluated. The polymer was used to solubilize paclitaxel, a chemotherapy medication. The Apisolex/paclitaxel formulation was well tolerated in test animals, demonstrating equivalent activity to paclitaxel on its own in terms of *in vitro* cytotoxicity, and *in vivo* tolerability. The lyophilized drug product was reconstituted in less than 30 seconds. Moreover, the process was shown to be more than 90% efficient, with a small particle size and narrow size distribution obtained. The Apisolex/paclitaxel formulation has further demonstrated more than 24 months' stability under ambient conditions to date, with no change in physicochemical properties.

In light of the technology's remark-

FIGURE 1

API / Excipient	Polysorbate 20	Polysorbate 80	Cremophor®[1]	Apisolex™
Amphotericin B	Fail	Fail	Fail	Pass
Cyclosporin A	Pass	Pass	Pass	Pass
Etoposide	Pass	Pass	Pass	Pass
Melphalan	Fail	Fail	Fail	Pass
Paclitaxel	Pass	Pass	Pass	Pass
BI-001[2]	Pass	Pass	Pass	Pass
BI-002[2]	Pass	Pass	Pass	Pass
BI-003[2]	Pass	Pass	Pass	Pass
BI-004[2]	Pass	Fail	Fail	Pass
BI-005[2]	Pass	Pass	Pass	Pass
API : Excipient Ratio	1 : 100			5 - 10 : 100

[1]Polyethoxylated castor oil (Kolliphor® ELP or Kolliphor EL, formerly known as Cremophor EL, is a registered trademark of BASF Corp)
[2]APIs for this study were provided by Boehringer Ingelheim Pharm. Inc.

Series A results for solubilization of APIs using Apisolex excipient compared to other standard industry excipients polysorbate 20, polysorbate 80, and Cremophor®.

FIGURE 2

API / Excipient	TPGS[1]	Captisol®[2]	PEG-PLGA[3]	Apisolex™
Amphotericin B	Fail	Fail	Fail	Pass
Cyclosporin A	Pass	Fail	Fail	Pass
Etoposide	Pass	Fail	Pass	Pass
Melphalan	Pass	Pass	Pass	Pass
Paclitaxel	Fail	Fail	Pass	Pass
BI-001[4]	Fail	Fail	Fail	Pass
BI-002[4]	Fail	Fail	Fail	Pass
BI-003[4]	Pass	Fail	Fail	Pass
BI-004[4]	Fail	Fail	Fail	Pass
BI-005[4]	Fail	Fail	Fail	Pass

[1]D-α-tocopheryl polyethylene glycol succinate
[2]Cyclodextrin (Captisol® SBE-AE-Beta-CD is a registered trademark of Ligand Pharmaceuticals Incorporated)
[3]Polyethylene glycol-poly lactic acid-co-glycolic acid
[4]APIs for this study were provided by Boehringer Ingelheim Pharm. Inc.

Comparison of APIs that were successfully solubilized by Apisolex excipient compared to other industry-standard excipients in "series B."

able capabilities, an approved oncology API reformulated with Apisolex excipient is currently under development by a pharmaceutical client. This project has progressed to the GMP manufacturing stage with clinical trials scheduled for 2023.

DRIVING CHANGE FOR PATIENTS

With the continued trend for poorly soluble new drug candidates – and the need to bring new cures to market for cancer and other diseases – novel solubilization approaches have never been more important. Excipients are a vital tool in this effort and in the industry-wide movement to make drugs more patient-centric. The power of novel excipients such as Apisolex polymer could revolutionize the parenteral drug development landscape, effectively solubilizing a wide range of APIs without compromising on safety or stability. Ultimately, this will be felt by patients as life-changing medicines that would otherwise fail in clinical development are now able to reach the market. ◆

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BIOGRAPHY

Joey Glassco is the Senior Global Market Manager for Injectable Drug Delivery at Lubrizol Life Science Health (LLS Health). She leads a cross-functional team to provide pharmaceutical excipient and contract development and manufacturing solutions to the pharmaceutical industry. She serves as the Director of Marketing for the CDMO division and was responsible for two new product launches. Prior to joining LLS Health, she spent nearly 15 years in marketing roles in various Lubrizol business units. She also has more than 10 years of experience in finance at Lubrizol, Ford Motor Company, and The Franklin Mint. She earned her Bachelor of Science degrees in Finance and Accounting from Juniata College and her MBA from the Smeal College of Business at Pennsylvania State University.

PLATFORM DEVICE

Alina: Shining the "Light" on the Benefits of a Platform Approach to Treating Chronic Conditions

By: Adam Stops, PhD

INTRODUCTION

Chronic diseases not only have a huge impact of the quality of life of patients and their extended families, but they also place a significant, and yet avoidable, burden on overstretched hospital infrastructures as well as the wider healthcare eco-system, including payers and pharmaceutical companies.

One such example of a chronic condition becoming increasingly burdensome is obesity. According to the most recent publication of the World Obesity Atlas, between 14%-17% of the world population aged over 5 years are living with obesity (BMI ≥ 30 kg/m^2). This means about 1 billion people are already affected by the condition. If the current trend persists, the incidence is expected to increase to 20% by 2030.[1] In the US alone, the medical care costs for this disease amount to $173 million, according to the Center for Disease Control and Prevention.[2] Despite these startling statistics, however, fewer than 3% of people with obesity are pharmacologically treated for it.

Closely linked to obesity is diabetes, in which it is believed 415 million people are living with diabetes globally, which is estimated to be 1 in 11 of the world's adult population. 46% of people with diabetes are undiagnosed and do not meet treatment goals for glucose lowering, which is key to managing their condition. This figure is expected to increase to 642 million people living with diabetes worldwide by 2040.[3] As a result, the estimated global direct health expenditure on diabetes in 2019 was $760 billion, a figure expected to grow to a projected $825 billion by 2030 and $845 billion by 2045.[4] Although there are differing estimates on the scale of spend, there is one consistent message – this is a significant challenge. Indeed, the spend on diabetes treatments makes it the third largest therapy area in terms of expenditure on drugs.[5]

MARKET TRENDS IN THE PREVALENCE OF DIABETES

There are three major market trends pharma organizations and their partners are currently wrestling with. First, as we have already acknowledged, obesity is a real challenge. Indeed, according to the World Health Organization, worldwide obesity has nearly tripled since 1975.[6]

Second, there is significant price pressure for insulin in the US even though the incumbent US Government has recently introduced the Inflation Reduction Act, to place a cap on insulin pricing for seniors on Medicare.

The third trend is the increased market access in developing countries, with data suggesting that by 2030, more than 80% of people with diabetes will live in what is currently called a "developing country."[7] Asia accounts for 60% of the world's diabetic population. As it has undergone rapid economic development, urbanization, and transitions in nutritional status in recent years, so too has it witnessed an explosive increase in diabetes prevalence within a relatively short time.

RECOGNIZING THE NEEDS OF PHARMA PARTNERS

Pharma innovation continues to play a key role in addressing the human and financial burden of managing chronic conditions, such as cardiovascular disease, gastrointestinal disorders, pain management, neurological disorders, and arthritis. We all understand the primary concern of pharma partners – to mitigate as much as possible, the risks associated with drug development, including safety, efficacy, cost, and time to market. The investment in time and money in development is such that every day counts, and so delays or worse, program failure, represents a significant risk. As indeed does delays in market launch or unforeseen costs, which may re-

sult in the end product not being as price competitive as anticipated.

ANSWERING THE CALL TO MITIGATE THE CHALLENGES OF CHRONIC DISEASES

According to the WHO, healthcare providers need to do more to engage patients in managing their own conditions and to use treatments properly. Several observers have also suggested that increasing the effectiveness of interventions to increase adherence may have a far greater impact on health than further improvement in biomedical treatment.[8]

The growing emphasis on self-administration of medication, for example, provides the means to ease the pressure on health services, improve compliance, and make everyday life more convenient for patients. And with the Covid-19 pandemic accelerating this trend as routine patient visits to healthcare facilities plummeted, pharma companies have intensified their focus on drug delivery devices patients can use in their own homes.

INTRODUCING A PROVEN PLATFORM TO ADDRESS THESE CHALLENGES

Key to the success of any drug delivery device are factors such as proven technology, low development costs, fast time-to-market, and a strong intellectual property (IP) position for the pharma company. Against this background, platform drug delivery devices have become more important than ever, providing an "off-the-shelf" choice that minimizes project risk and avoids the requirement for an up-front investment of millions of dollars to fund the development of new bespoke devices. Instead, the availability of customization options to suit a variety of different drugs and primary packaging with minimal change in components keeps costs down and offers faster time-to-market, enabling patients to benefit from new therapies sooner rather than later.

Alina® Pen Injector Platform

Stevanato Group's Alina® pen injector is an example of a platform device for variable and multi-dose treatments for chronic conditions. With three different configurations, the platform meets an emerging and important market demand to exploit one single platform for different treatments.

The benefits of a single platform device for pharma partners cannot be underestimated as they are wide ranging in terms of mitigating risk, time, and cost. We will explore each of the benefits in more detail, knowing the Alina platform enables combination products to be launched with a more cost-effective and streamlined approach.

THE BENEFITS OF A PLATFORM APPROACH ARE WIDE RANGING FOR PHARMA PARTNERS

As an established combination product platform with proven technology, the mitigation of risk is a key feature. Quite simply, all the significant hurdles and roadblocks have already been navigated by the in-house device development teams. A positive consequence of reduced risk is of course an accelerated time to market as the product used in clinical trials will be exactly the same specification as the marketed product. There is a wide held view that adherence within clinical trials is not anywhere near optimum, and as a result, the level of dosing can come under scrutiny, a challenge entirely eradicated with products such as the Alina pen injector.

Increases in risk and time inevitably lead to greater costs, another element that is then mitigated by using an established platform that features a ready-to use, standardized, rapid to implement technology-transfer package to ensure quality of delivery and the simplification of processes.

While there is a great deal of standardization in the platform, that is not to say there is no flexibility. The Alina pen injector can be used for different applications as it can deliver a range of different maximum doses – enabling pharma partners to maximize the benefit of a singular platform for several different treatments – another tangible way in which risk, time, and cost can be managed effectively.

The Alina platform also features a

"Key to the success of any drug delivery device are factors such as proven technology, low development costs, fast time-to-market, and a strong intellectual property (IP) position for the pharma company. Against this background, platform drug delivery devices have become more important than ever, providing an "off-the-shelf" choice that minimizes project risk and avoids the requirement for an up-front investment of millions of dollars to fund the development of new bespoke devices."

range of branding and customization options, which means that, as an example, individual colors can be selected for each market segment. As we have already acknowledged, there are real and timely opportunities for pharma; however, sometimes the points of differentiation may be limited, for example, in the generics market, and therefore branding can be a key contributor to a successful market launch.

Design for manufacturing and ease of final assembly have also been considered to optimize the production process. The device is manufactured at Stevanato Group's FDA-inspected facility in Germany, where access to tooling and sub-assembly equipment is available to clients aiming to maximize the return on investment in their device programs and reduce time to market. Dedicated production tooling and lines are available on request for customization or to support overall risk mitigation strategies.

Alina is fully compatible with Stevanato Group's range of glass cartridges – such as bulk and ready-to-use EZ-fill® cartridges – as well as the company's final assembly equipment. Moreover, Alina is compatible with a variety of fill-and-finish systems.

One big concern for pharma is whether a device can go from bench to large-scale manufacturing at a cost and time the market can bear. The Alina platform is supported by all the documentation and rigor required to deliver a standard of quality that reassures the regulatory authorities. And because the platform is established, scalability through the development lifecycle from trials to maturity is readily managed for all kinds of customers, from start-up biotech's to global pharma partners. And of course, as the manufacturing infrastructure is built, customers do not necessarily need to invest in potentially expensive device design, tool sets, and assembly and sub–assembly equipment or testing.

Alina can be provided as a flexible device platform because, as a full solution provider, Stevanato Group has a deep understanding of how pharmaceutical products, containers, closures, and drug delivery devices interact with each other and work together to form a cohesive system. This holistic approach means pharma companies looking for customized drug delivery and containment solutions can benefit from tailored solutions that combine products and technologies into a coherent, integrated offering.

Indeed, Alina was developed to address the need to reduce the complexity of the supply chain, and this philosophy of efficiency is applied to all processes relevant to the development of a combination product, from initial concept through to its launch on the market.

From a patient perspective, the device has a user-friendly design to improve patient experience. It is intuitive for patients, with minimal user steps, and is designed to give confidence and reassurance. To help patients select the right dose, Alina has only one number visible in the dosing window at any given time, and the dose can be corrected with a simple dial back. Patients receive visual, audible, and tactile feedback for dose setting, correction, and injection, and the injection force is optimized for patient comfort.

SUMMARY

Diabetes and obesity can be regarded in some quarters as a global public health crisis that threatens the economies of all nations, particularly developing countries. Fuelled by rapid urbanization, nutrition transition, and increasingly sedentary lifestyles, the diabetes epidemic has grown in parallel with the worldwide rise in obesity. Asia's large population and rapid economic development have made it an epicenter of the epidemic.

Post pandemic, there has been a

growing emphasis on self-administration of medication. Not only does this relieve the pressure on health services, it also makes life considerably easier for patients and improves regimen compliance. In order to maximize the present opportunities, pharma companies are increasingly looking to adopt a platform approach to development in which proven technology, low development costs, fast time-to-market, and strong IP are all delivered.

The Alina platform is one such solution that combines enhanced patient-focused features while mitigating the time, risk, and cost traditionally associated with product development. At every stage of the development lifecycle, from small batch clinical trials to industrialization and large-volume manufacture, the Alina platform and Stevanato Group's expertise and experience enables pharma partners to realize the potential of the market and enable millions of patients to access high-quality therapies. ◆

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BIOGRAPHY

Dr. Adam Stops is Head of Product Management for Drug Delivery Systems at Stevanato Group, managing auto-injectors, prefilled variable and fixed-dose pen injectors, large-volume wearable injectors, and inhalers. He earned his PhD in Mechanical Engineering and his MBA in Business Management. He has broad experience in the design, development, and product management of devices and parenteral products, and has worked with innovative multinational companies, leading teams of experts in device research, design, and industrialization throughout his career.

CLINICAL TRIALS

How Conversational Data & Listening at Scale Improve Clinical Recruitment

By: Amy Brown

INTRODUCTION

It's no secret clinical trials have a recruitment problem. Research shows 85% of trials fail to retain enough patients. Recent news revealed COVID trials lacked diversity and female representation — fewer POC were recruited, and it's common for women to be underrepresented in trials because of the potential risk to their fertility or impacts on future pregnancy.

Recruiting more diverse clinical trial participants shouldn't be a secret — nor is it a problem to ignore. Without representation from all populations, researchers fail to gather the data needed to fully understand the effects of the drugs they're developing.

One of the most effective ways to gather valuable, relevant, and useful information from a clinical trial is by listening to conversations at scale. This approach isn't just valuable for understanding participants' mindsets. It also helps researchers understand the psychosocial factors influencing and affecting a specific patient population.

Organized conversational data can answer questions about patient frustrations and fears and uncover transportation challenges; caregiver, familial, and societal factors; and other social determinants of health (SDOH) impacting patients' participation in a trial.

By listening to their participants at scale, life science companies can improve their clinical trial recruitment success, seeking underrepresented populations with more intentionality.

WHY LISTEN

Listening to recorded conversations between participating providers and patients has the potential to generate incredible value in understanding the mindset of patients diagnosed with specific illnesses, conditions, or diseases. During these emotional conversations, patients' vulnerabilities, fears, and questions surface.

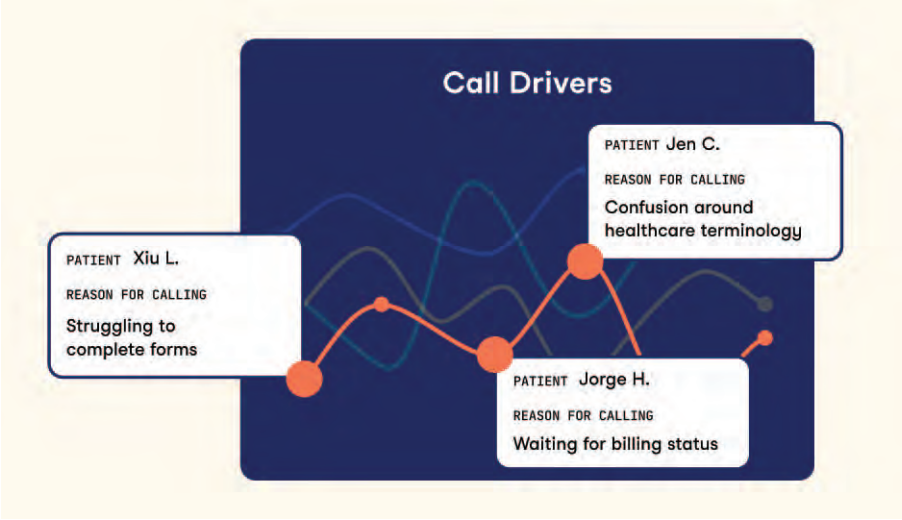
Currently, this area of research uses structured data sources like lab, clinical, and claims data. We have a good sense of improving comorbidities and how clinical diagnoses can lead to certain health outcomes. Where we've not had enough innovation is in understanding the psychosocial factors of healthcare. Conversational data offers a wealth of insight to better understand participants in their own words.

Using AI, organizations can listen at scale to surface patient emotions. Machine learning algorithms can be trained utilizing both text and sound wave analysis to detect tone and intent, which can indicate certain emotions like frustration and confusion. There are nuances in understanding the difference between these emotions and the implications on how your patient population responds.

This active feedback is critical because listening gives in-the-moment feedback, whereas surveys and other data-driven sources are after-the-fact. They're an aggregate of the whole — which is important — but you lose the individual voice. One of the most important things we can do is to deeply understand the lives of the patient population — and be very intentional about seeking out populations underrepresented in the data source.

RECRUITING WITH INTENTION BECAUSE REPRESENTATION MATTERS

The US government has recommended changes to drive compliance and reward increased representation in clinical trials as well. The Committee on Improving Representation of Women and Underrepresented Minorities in Clinical Trials and Research



offered several recommendations to recruit with intention. They included the following:

- Forming a new Department of Health and Human Services task force to examine equity in research and ensure proper data collection.
- Implementing new FDA requirements for recruitment plans when submitting an application for investigating a new drug or new device exemption application.
- Standardizing requirements for submitting demographic data to the ClinicalTrials.gov database.
- Updating the coverage guidelines considering representation from the Centers for Medicare and Medicaid Services.

Accelerating representation, recruitment, and retention of diverse patients relies on the sponsors, study sites, and investigators. Sponsors, particularly, can help clinical development teams understand the barriers to participation and retention by first defining and then identifying the targeted patient populations.

By looking through the lens of emotions and diverse topics, you can tease out the SDOH from that data source — data that helps sponsors identify which patients to vet for clinical trial participation. Sponsors also gain a complete picture of the demographic, geographical, and social factors causing hesitancy and confusion.

INEQUITIES IN HEALTHCARE R&D

Treatment regimens researchers find effective in clinical trials can't necessarily be applied confidently to all populations if certain groups lack adequate representation during those trials. For example, the human clinical trials for the COVID vaccines had an insufficient number of Black and Asian participants. Lower numbers led to vaccine hesitancy among these populations. Other examples that lacked representation included studies for breast cancer, new asthma medication, blood thinners, and seizure drugs.

But part of the challenge in attracting historically marginalized groups to participate in clinical trials has come from limited racial reporting, the underutilization of available medical resources, and hesitancy or mistrust in the medical system.

The US Congress recently commissioned a report, Improving Representation of Women and Underrepresented Minorities in Clinical Trials and Research, to study the severity of underrepresentation. The report discovered that while progress has been made with the inclusion of white women, racial and ethnic minority populations continue to be left out of clinical research and trials, as have:

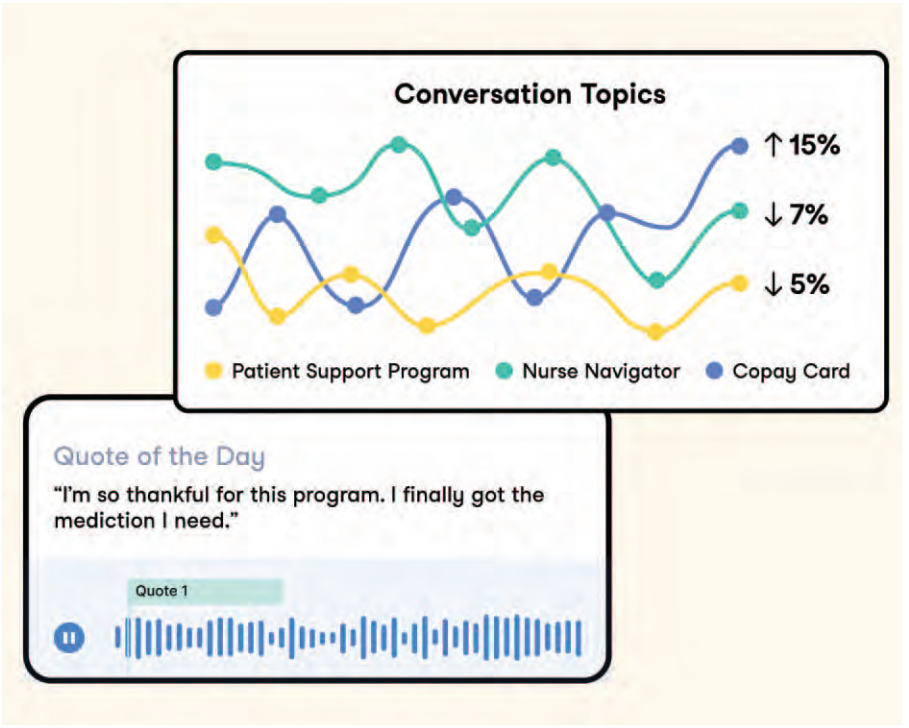
- Members of the LGBTQIA+ community
- Older adults
- Pregnant and lactating individuals
- People with disabilities

BARRIERS TO RECRUITING PATIENTS FOR CLINICAL TRIALS

Many factors contribute to the challenge of finding patients to participate in clinical trials. The number of drugs in the market is increasing, and saturation has contributed to the dwindling pool of potential subjects.

Many trials fail to reach their recruitment goals. Phase 1 and 2 trials need hundreds of patients, and some Phase 3 trials require thousands of patients. Yet up to 85% of clinical trials may not reach those targets within the specific time period. Other barriers include the following:

- Financial limitations
- Insufficient infrastructure support
- A lack of physician awareness about current trials
- A lack of appropriate trials for community-based settings
- The patients' negative beliefs or atti-



tudes toward research

Successful patient criteria requires designing a trial reflecting patient needs while continuously keeping the patient's perspective in mind. And the more transparent you are during the recruitment process, the better — even though that transparency is difficult to achieve.

Listening to conversational data, however, can help researchers not only recruit participants but also evaluate whether the trial, once underway, addresses the symptoms and challenges patients find meaningful. These conversations capture what's top of mind for patients, including the clinical trial's goal, why one trial is preferred over another, and whether the clinical trial is researching the cure for their condition — or new treatment options.

Communication is key during the recruitment process. Patient recruitment strategists must review protocols, verifying whether the endpoints are adjustable once the trial launches and that the trials meet patient needs. For example, benefits of participation might include receiving care from an expert in their condition — or having the opportunity to help researchers learn.

PROVIDING PSYCHOLOGICAL SAFETY & CULTURAL COMPETENCY

Psychological safety and cultural competence are essential for including diversity in clinical trials. Psychological safety encompasses the belief that everyone is safe from judgment, humiliation, or punishment if they speak up, ask questions, or admit a mistake.

Cultural competency includes recognizing a practitioner's biases, power imbalances, and barriers impeding effective clinical care. It involves recognizing and acknowledging disease incidence and prevalence, unique health beliefs, and treatment outcomes in diverse populations.

It also introduces the idea of cultural humility. That is, a healthcare practitioner or researcher in a clinical trial recognizes the differences in cultural values and doesn't assume one or another is the norm. Organizations and individuals embracing cultural competency intentionally minimize the impact of implicit biases and work to eliminate their own unconscious biases.

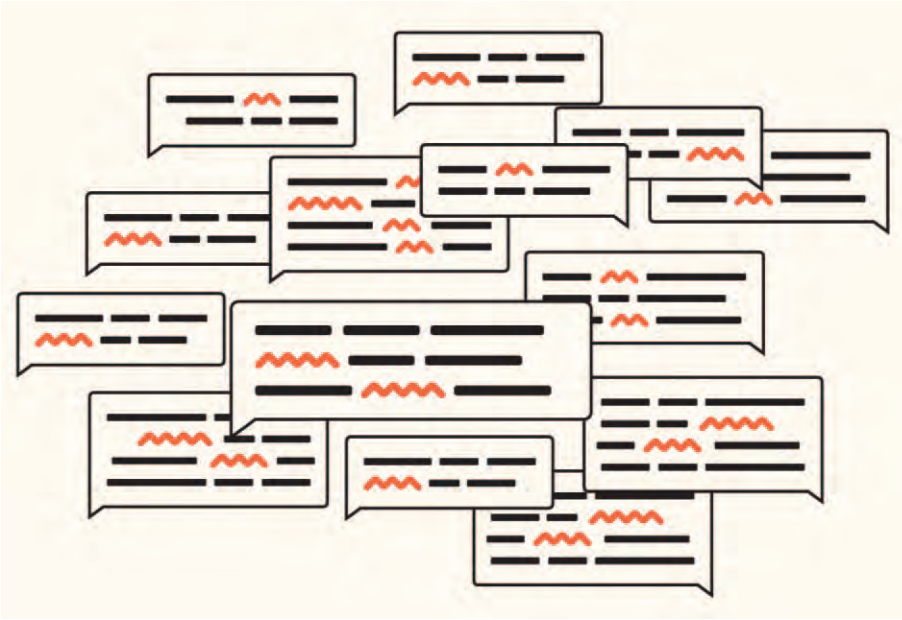
Conversational data uses ML algorithms designed to detect words indicating emotion and nuances of tone helping to inform training needs. With conversational data, you can listen for phrases like:

- "I'm excited."
- "I'm hopeful."
- "I'm fearful."
- "I have questions, but I know I need to explore something that might be in a clinical trial rather than try something already available commercially."

By analyzing conversational data in combination with participant demographic data, organizations can also identify concerns expressed by a specific community. Listening at scale provides additional context that enhances already gathered demographic data. Addressing those concerns sooner shows transparency, helps build trust, and can increase someone's willingness to participate in a trial.

Listening directly to the voice of the customer facilitates an even more granular analysis of understanding how tone, paired with words, may indicate specific emotions. For example, in the commercial space, the top two negative emotions conversational data most commonly identified are frustration and confusion. These emotions have certain implications depending on whether your patient population is frustrated or confused.

Instances of noted confusion include a possible messaging problem or the need



for enhanced clarity on directing patients' next steps. Frustration implications are a bit different and refer to a CX or journey problem in which a participant is unsure what to do despite trying to call and communicate with the provider.

But applying a generic label of negative sentiment isn't good enough for figuring out what that negative sentiment means — or what to do about it. Focusing the research and data science work on diving more deeply beyond a sentiment score and pairing those emotions with the conversation's key topics creates a more holistic picture that allows organizations to understand at scale.

A single data point of negative sentiment doesn't provide enough context for clinical trial sponsors to address potential participant concerns. But direct, voice-of-the-customer conversations allow organizations to pinpoint with precision what factors are driving the caller's emotion and gain valuable insights and feedback.

You must listen to patient perceptions because learning about those experiences is the best way to deepen that understanding. Unstructured conversational data:

- Identifies SDOH and other social pressures patients — and potential trial participants — face.
- Pinpoints quality and access indicators, helping clinical trial designers to find the most effective ways to improve participant satisfaction.
- Analyzes different interactions to identify challenges, mitigate risks, and refocus communications and programming.
- Identifies training opportunities and areas of improvement — and positive recognition.

Life sciences organizations and drug companies need to continue their efforts to make care more accessible, starting with populating clinical trials in all phases with more diverse participants. You can't get the health outcomes you want without seeking the truth of the human side of the equation.

THE PATH FORWARD

The incredible value of listening to patient voices in a new, different, scalable way provides strategic value to those planning and conducting clinical trials. Drug companies empowered to listen to their potential trial participants will be more informed, empathetic, and enlightened when approaching the task of populating trials. The result? Trial programs will be more prepared to recruit and serve subjects that more closely reflect the diversity of the patients the drugs are designed to treat. ◆

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

BIOGRAPHY

Amy Brown is the Founder and CEO of Authenticx – the software platform analyzes and activates patients' voices at scale to reveal transformational opportunities in healthcare. She built her career as a rising executive in the healthcare industry, during which time she advocated for underserved populations, led and mobilized teams to expand healthcare coverage to thousands of Indiana residents, and learned the nuance of corporate operations. In 2018, she decided to leverage her decades of industry experience to tackle healthcare through technology. She founded Authenticx with the mission to bring the authentic voice of the patient into the boardroom and increase positive healthcare outcomes.

ANTI-VIRAL RESEARCH

Anti-Viral Activity of *Pimpinella anisum* Extract *In Vitro* Study

By: Fouad Al-Bayaty, Mazen M. Jamil Al-Obaidi, Maryam Haki Al-Doori, and Omar Imad

INTRODUCTION

In the tropics and subtropics, dengue fever is one of the utmost dreaded vector-borne flavivirus illnesses due to its rising prevalence. 55% of the world's population, or 3.6 billion people, are at a higher risk of contracting dengue virus (DENV) infection, according to worldwide estimates. Dengue fever is estimated to affect 390 million people each year, with 96 million cases involving dengue hemorrhagic fever or dengue shock syndrome (DSS) and 300 million cases involving moderate or asymptomatic illnesses.[1] Recent WHO categorization categorizes the disease as dengue without warning symptoms (DWOS), dengue with warning symptoms (DWWS), and severe dengue.[2] A DWOS DENV infection may be asymptomatic or manifest as a "flu-like illness," but (DWWS) is distinguished by a rapid onset of fever accompanied by non-specific signs and symptoms, such as back pain, headache, flushed facial skin, and stiffness.[3] Leaking plasma and a low number of platelets can kill people with severe dengue infections, especially after hypovolemic shock.

For viral infections, herbal therapies, including traditional Chinese medicine, have also been proposed as alternatives.[4] Due to their multivalent properties, they are typically safer than chemical medications and are less likely to cause resistant infections. Moreover, a number of herbal remedies may target both the virus and the signs of DENV infection, some of which are caused by the viral-induced overproduction of inflammatory mediators, such as cytokines.[5-8] *P. anisum* is an Apiaceae flowering plant endemic to India and southwest Asia.[9] A 1-m annual herbaceous plant, the lower leaves are simple, 2-5 cm long, and shallowly lobed, whereas the upper leaves are feathery pinnate and formed of many leaflets. The 3-mm white flowers are in dense umbels. The fruit is a 3-5-mm long, oblong, dry schizocarp.[10] *P. anisum* has been utilized as a medicinal plant for its stimulating impact on digestion, antiparasitic, antifungal, and antipyretic properties.[11,12] In addition, it has demonstrated anticonvulsant properties and has been used to treat constipation and possesses anti-ulcer properties.[13-15] Recent reports indicate its oil possesses antioxidant and antibacterial properties.[16] There are limited reports of *P. anisum's* antiviral activity. Therefore, this study was done to evaluate the antiviral effectiveness of this plant against dengue virus.

MATERIALS & METHODS

Plant Specimens

Ethno Resources Sdn Bhd in Selangor, Malaysia provided the seeds for *P. anisum*. By contrasting them with the voucher specimen kept in the Herbarium of Rimba Ilmu at the Institute of Science and Biology of the University of Malaya in Kuala Lumpur, they were verified.

Ethanol Extraction

The crude-dried extract was made by extracting 100 grams of plant material for 48 hours in 900 mL of 95% ethanol, then filtering and evaporating the ethanol extract under low pressure with a Buchi-type rotary evaporator. It was determined the yield of ethanol extracts was 7.2% (w/w).

In Vitro Antioxidant Screening

DPPH Radical Scavenging Activity Assay: The 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical was used in the modified technique to measure the antioxidant activity of plant extract based on an electron transfer reaction between the DPPH reagent and the plant extract.[17] Five separate concentrations were obtained by diluting a stock solution (1 mg/1 mL) of the plant extract and the antioxidant standard (gallic acid) to five different concentrations. DPPH was mixed with five mL of plant extract and standard (195 mL). After that, the combination was incubated at 37°C for 30 minutes. The absorbance value was measured at 517 nm using a UV-1601 spectrophotometer (Shimadzu, Japan).

Ferric Reducing Antioxidant Power Assay (FRAP): FRAP was completed using Erel's previous method.[18] The FRAP reagent was made using a 1:1:10 ratio of 300-mmol/L acetate buffer (pH 3.6), 10-mmol/L 2,4,6-tri [2-pyridyl]-s-triazine (TPTZ) in 40 mmol/L HCl, and 20-mmol/L FeCl3 at 37°C. TPTZ working reagent served as the blank solution, while ferrous sulphate heptahydrate (FeSO4*7H2O) served as the standard. The standards (300 mL) and the sample solution (10 mL, 1 mg/mL of plant extract) were combined with FRAP reagents. The mixture was incubated at 37°C for 0 to 4 minutes before the absorbance at 593 nm was spectrophotometrically determined. The data were then shown as the moles of gallic acid contained in 1 mg of extract.

Phytochemical Screening

Total Phenolic Content (TPC) & Total Flavonoids Content (TFC): The total phenolic components of ethanol plant extract were measured using a modified version of the prior approach, and the total flavonoids content (TFC) was assessed using Chang et al aluminum's chloride colorimetric method.[19,20]

Cytotoxicity

For this test, the American Type Culture Collection provided the Hs888Lu cell line, which is a human normal lung fibroblast cell line (ATCC, The Global Bioresource Centre, Manassas, VA, USA). Using the Promega Cell Titer 96 Aqueous Non-Radioactive Cell Proliferation (MTS) assay, the cytotoxic potential of the *P. anisum* extract was evaluated.[21] First, Hs888Lu cells were grown in Dulbecco's Modified Eagle's Medium (DMEM; Sigma, USA), which has a high glucose content, 1% non-essential amino acids (PAA Laboratories GmbH, Austria), 2% L-glutamine (200 mM), 1% penicillin/streptomycin (100 times), and 1% sodium pyruvate (FBS, PAA Laboratory GmbH, Austria). The Hs888Lu was incubated at 37°C in an incubator (Contherm Scientific Ltd., New Zealand) with 5% CO2 and 95% humidity. The cell lines were seeded (1 x 10^5 cells/mL) on a 96-well plate and cultured for 24 hours at 37°C in a moistened environment before being added to the plant extract. The diluted extract solution, ranging from 100 to 500 g, was applied in triplicate to the culture plate, which was then cultivated for 24 hours under the same circumstances. After the treatment, each of the 96 wells received 20 mL of 37°C-prewarmed MTS reagent, and the plate was incubated for 3 hours at 37°C. The Glomax multi-detection system was used to measure the absorbance at 492 nm (Promega, USA).

Anti-Viral Activity of *P. anisum*

Dengue Virus: The Dengue virus type-2 was propagated in confluent C6/36 cells. Briefly, the medium was discarded, and the virus stock was added slowly and gently. It was then incubated at 37°C for 1-1.5 hours. Post-infection, L-15 medium supplemented with 2% FBS was added post-infection and incubated at 30°C. Cytopathic effect (CPE) was examined daily, and the virus was harvested when most of the cells showed CPE. The content of the flask was spun down, and the supernatant, which contains the virus, was aliquoted and stored at -80°C.

Sample Preparation: Vero cells were plated at a density of 5.0 104 per well in a 24-well plate and incubated overnight. Three different types of treatment were used, namely pre-, simultaneous-, and post-treatment. For pre-treatment, the extracts were first added 24 hours prior to the infection. For simultaneous treatment, both the virus and the extracts were added simultaneously, while the extracts were added 24 hours after the infection was established. After that, the plates were kept in an incubator for three days at 37°C. The supernatant and the attached cells were harvested and subjected to RNA extraction.

RNA Extraction: RNA was extracted from the samples using the Bioneer Viral RNA extraction kit. Briefly, 200 mL of sample and 400 mL of binding buffer (VB) were added and vortexed for 10 seconds. Following a 10-minute incubation at room

TABLE 1

	P. anisum	Gallic Acid
FRAP	1134.42 ± 0.1	1503.44 ± 0.3
DPPH	71.39 ± 0.71	77.31 ± 0.83
TPC	495.56 ± 0.090	
TFC	0.435 ± 0.0298	

Antioxidant activities FRAP, DPPH, TPC, and TFC of the *P. anisum*.

temperature, 100 mL of isopropanol was added to the mixture. Vortex and quick spin for 10 seconds before transferring the content into the spin column provided. The 500 mL of washing buffer 1 (W1) was added and rotated at 8,000 rpm for 1 minute, followed by the addition of 500 mL of Washing Buffer 2 (W2) and spinning at 8,000 rpm for 1 minute. The column was further spun at 13,000 rpm for 1 minute before the column was transferred into a new tube. After adding 30 mL of elution buffer and letting it sit for 5 minutes at room temperature, the tube was spun at 8,000rpm for 1 minute.

Real Time-PCR: The antiviral properties of the extracts were determined using real-time PCR. For Dengue virus, the primer sequence and procedure described in the reference were utilized.[22] The thermal cycling parameters were reverse transcription for 30 minutes, Taq activation for 15 minutes, 35 cycles of denaturation for 30 seconds at 94°C, annealing for 40 seconds at 60°C, elongation for 50 seconds at 72°C, and a final elongation for 10 minutes at 72°C, followed by a hold for 4°C.

Statistical Analysis

The t-test was used to examine all *in vitro* test results, which are reported as mean SEM. All *in vivo* test results are shown as mean standard error of the mean, and they were analyzed using one-way ANOVA and Tukey's post-hoc test in the Statistical Program Sciences version 20 (SPSS Inc, USA). The statistical significance of the differences between the means is determined by whether or not the p value is less than 0.05.

RESULTS

Evaluation of Antioxidant Activities & Phytochemical Screening

The FRAP value of *P. anisum* was 1134.42 ± 0.1 mmol/g, which is lower than the standards for gallic acid, 1503.44 ± 0.3 mmol/g (Table 1). The positive control and plant extract DPPH free radical scavenging findings, on the other hand, are presented as a percentage of inhibition. The DPPH of the *P. anisum* was 71.39 ± 0.71 inhibition, while the standard gallic acid was 77.31 ± 0.83 inhibition, respectively. The TPC of the *P. anisum* was 495.56 ± 0.090 mg/g, while the TFC value was 0.435 ± 0.0298 mg/g. This suggested that *P. anisum* contained sufficient antioxidant efficacy.

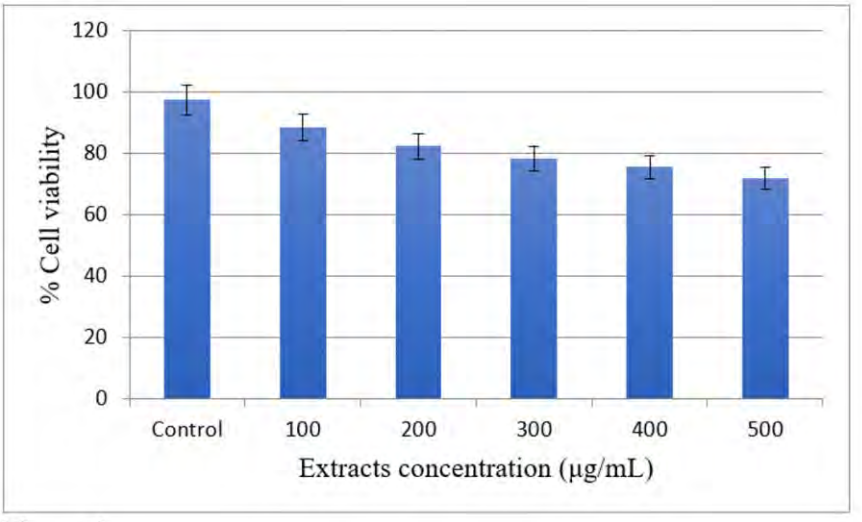
Cytotoxicity Screening

Figure. 1 summarizes the findings of *P. anisum* cytotoxic activity, which was represented as a percentage of the value seen with no plant treatment (control). Normal lung cells were not killed by any of the plant extract concentrations, as can be seen in Hs888Lu.

Evaluation of Antiviral Activity of *P. anisum* Against Dengue

P. anisum was evaluated for antiviral activity against dengue virus and is summarized in Figure 2. *P. anisum* exhibits anti-viral activity against dengue at con-

FIGURE 1



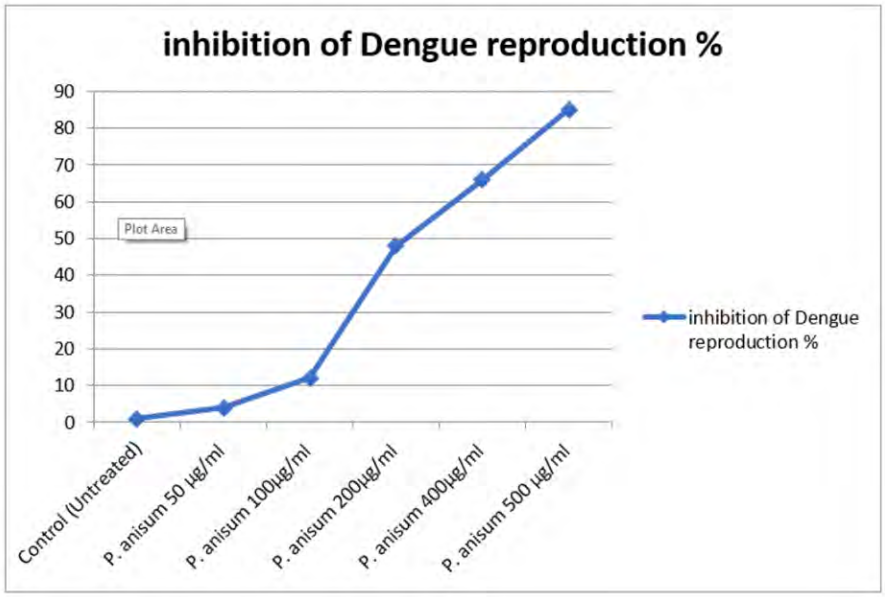
Cytotoxic activity of *P. anisum* in normal lung (Hs888Lu) cell line at different concentrations and 24-hour exposure time. Values are reported as the mean ± S.E.M. and were analyzed by t-test. The differences between means were considered statistically significant when the p < 0.05.

centrations of 200 g/ml to 500 g/ml, which could inhibit the virus' reproduction.

DISCUSSION

A FRAP test was performed to examine the antioxidant components of *P. anisum* free radical scavenging activity. This technique was created by Huan et al.[23] During the procedure, an antioxidant, such as polyphenol (ArOH), may provide a single electron. The blue Fe (II)-TPTZ complex is decreased from the Fe (III)-TPTZ complex, which is then detected at 700 nm. Antioxidant chemicals, such as polyphenol, which function as reducing agents, exert their impact by donating hydrogen atoms to the ferric complex, therefore interrupting the Fe (III)-TPZ radical chain reaction. Depending on the reduction potency of each antioxidant sample, test solutions changed color from bright yellow to green or dark blue after the reaction. In vivo, the FRAP assay has been criticized for its low pH, which may inhibit electron transmission. The antioxidant activity of ferric (Fe3+) is too reliant on its capacity to decrease iron, which is a downside of its usage.[24] The Fenton Reaction describes how *P. anisum* may protect against oxidative damage by eliminating ferrous ions (Fe2+) that can participate in hydroxyl radicals. By suppressing the generation of reactive oxygen species and lipid peroxidation, reducing ions (Fe2+) protect against oxidative damage. Furthermore, the significance of the DPPH test in determining the free radical scavenging ability of several antioxidants has been highlighted by Ozcelik.[25] The presence of phytochemicals is a common indicator of antioxidant action. A higher content of alkaloids, phenolics, flavonoids, terpenoids,

FIGURE 2



Antiviral activity of *P. anisum* against dengue virus by RT-PCR. Values are reported as the mean ± S.E.M. and were analyzed by t-test. The differences between means were considered statistically significant when the p < 0.05.

and other phytochemicals was associated with higher antioxidant activity.[26] The presence of TFC and TPC in *P. anisum* phytochemical screening explains its scavenging activity. Similarly, it was discovered that *P. anisum* seed is a powerful antiperoxidative agent and has a wide range of applications and uses in the food and pharmaceutical industries.[27] Therefore, the findings of the DPPH experiment demonstrate the antioxidant activity of *P. anisum* is attributable to the presence of phytochemicals in its content. Interestingly, it has been demonstrated that the antioxidant and antibacterial effects of *P. anisum* extracts can be related to their phenolic content because several phytochemical investigations have revealed that *P. anisum* contains considerable levels of phenolic chemicals.[28,29] We may deduce from the findings of these two antioxidant assays that no one antioxidant test delivers the best results as various assays may yield different kinds of antioxidant capabilities. This is due to the fact that in theory, neither a specific combination of phytochemicals nor a specific individual component can be attributed to having overall antioxidant activity. Consider the antioxidant capacity when all antioxidants contribute to the antioxidant activities by acting synergistically or additively. Much of the antioxidant scavenging action is determined by the quantity and type of antioxidant chemicals as well as the polarity of the solvents. Yu et al have found that the polarity of a solvent affects the antioxidant properties of a specific group of antioxidant compounds and changes how well the solvent works with molecules from that group.[30]

To analyze the toxic effect of a plant on human health, it is necessary to examine the toxicity of a plant extract. The data showed no cytotoxicity against the Hs888Lu cell line. This result was consistent with a previous study that showed MTT and LDH experiments demonstrated ethanolic extract had cytotoxic action against the human prostate cancer cell line at quantities deemed safe for normal rat skeletal muscle cells.[31] As previously mentioned, traditional medicine is used by

a large number of people in developing countries for their primary healthcare needs. Numerous illnesses, including ulcers, wound healing, and hyperlipidemia, are treated with medicinal herbs.[32] The flavonoid content of the plant extract suggested that *P. anisum* had substantial antiviral activity against DENV *in vitro*. Indicators of selectivity for *P. anisum* when infected cells or uninfected cells were treated with 200, 400, or 500 g/ml, respectively. The observed discrepancies in *P. anisum* concentration levels may be the result of intracellular *P. anisum* accumulation during therapy. At a low concentration, however, a minor influence on the activity of *P. anisum* was also found. These results imply the predominant anti-dengue activity of *P. anisum* is probably related to its action alongside the various phases of intracellular reproduction of DENV, as opposed to early stages of the virus's replication cycle, such as viral attachment or entrance. *P. anisum* suppresses DENV replication, and the considerable decrease in DENV-specific RNA proposes that *P. anisum* may also target the viral replication machinery, specifically by inhibiting RNA polymerase. According to reports conducted by Ibrahim, waste residues of *P. anisum* are prospective new sources of phenolic antibacterial chemicals, offering the pharmaceutical sector new economic prospects.[33] They propose that combining *P. anisum* waste extracts with some antibiotics yields a novel option for treating infectious disorders. Also, Schnitzler discovered the antiviral action of anise oil on enveloped viruses.[34] *P. anisum*, on the other hand, was stated to be efficient against herpes viruses; it is more specific for HSV-1.[35] However, the effects of various plant extracts on cellular RNA polymerases and the formation of complexes with RNA have been described, indicating they may similarly alter the replication enzymes.[36] Lastly, three antiviral and immune-stimulating compounds (LC1, LC2, and LC3) were identified from a hot water extract of *P. anisum* seeds. LCs demonstrated antiviral activity against HSV-1 and 2, HCMV, and measles virus.

CONCLUSION

The present study demonstrates *P. anisum* showed significant antioxidant activity by DPPH and FRAP, which may be due to the contents of TPC and TFC, which are considered potent antioxidants. The cytotoxic activity and acute toxicity of *P. anisum* did not show any signs of toxicity *in vitro*. Antiviral results showed that *P. anisum* has antiviral activity in a dose-dependent manner. ◆

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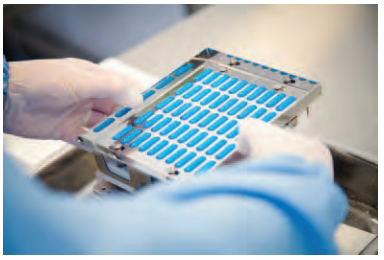
Bionex's mission is to realize the applications of biopharmaceutical and life sciences into commercial products and services that benefit human health. We specialize in the formulation and development of novel topical, transdermal/transmucosal, implant, and nasal/inhalation drug delivery systems. We offer out-of-box, cost- and time-efficient CRMO services: pre-formulation; dosage form design; product innovation, product life-cycle management; integration with analytical chemistry, product stability study; clinical supply manufacturing, process development and optimization; IND-CMC package readiness and submission; full support for quality system, technology transfer, regulatory and patent filings. Bionex capabilities are its expertise in formulation science and analytical chemistry, full range of formulation/processing, analytical, and testing capabilities in cGMP facility, and well-connected network of industrial, academic and business consultants and advisors. For more information, visit Bionex at **www.bionexpharma.com.**

Analytical Formulation & Development Services



Catalent, a global leader in formulation and development, offers a broad array of analytical solutions for small and large molecules. With extensive laboratory and stability chamber capacity, industry-recognized experts, and a suite of services ranging from compendial to extractables and leachables testing, Catalent provides tailored analytical solutions for stand-alone projects, and can help its partners advance their molecules from development to commercialization. Catalent's US and European locations provide global solutions for a wide range of dosage forms, with specialized capabilities in handling challenging molecules, including controlled substances, highly potent compounds, as well as temperature, light, pH or oxygen-sensitive APIs. For more information, contact Catalent Pharma Solutions at (888) SOLUTION or visit **www.catalent.com.**

Drug Delivery Platform

For pharmaceutical companies developing sustained-release drug delivery strategies, **Celanese** offers the VitalDose® Drug Delivery Platform, providing long-acting controlled release of small molecules, biologics, and RNA through implant and insert dosage forms. Work closely with experts in the Celanese Development & Feasibility Lab for customized program support including development services, material supply aligned with GMP principles, and regulatory support tailored to your application—helping you establish proof of concept. Learn more at vitaldose.com. For more information about solutions for the VitalDose sustained drug delivery platform, visit **vitaldose.com.**

Development & Manufacturing Solutions

Emergent CDMO is dedicated to helping pharma and biotech innovators bring lifesaving therapies to patients from around the world. Our integrated development and manufacturing network can support early to late-stage production of biotherapeutics and vaccines. Whether you're looking for initial process development support, small volumes of material for clinical trials, or large-scale production for a global commercial therapy, our experienced CDMO team is ready to serve as your trusted guide from molecule to market. We support a broad portfolio of preclinical through commercial programs with experience in a wide range of platforms and technologies including mammalian, viral, and p lasma proteins. For more information, visit Emergent CDMO at **www.emergentcdmo.com.**

Hands-On Formulation Support

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

Integrated Contract Manufacturer

Jubilant HollisterStier is an integrated contract manufacturer of sterile injectables, ophthalmics, otics and sterile and non-sterile topicals and liquids. Our facilities in North America provide specialized manufacturing for the pharmaceutical and biopharmaceutical industries. We provide a full-range of support and services to streamline the manufacturing process such as on-site assistance from process qualifications through product release. With over 100 years of manufacturing expertise with a global reach, our team is committed to meeting your project's milestones efficiently. For more information, visit Jubilant HollisterStier at **www.jublhs.com.**

Fully Integrated CDMO

Lifecore Biomedical is a fully integrated CDMO offering expertise in specialty formulation, aseptic filling, and final packaging of both complex medical devices and injectable pharmaceuticals. We currently manufacture FDA-approved commercial products at our three cGMP facilities and have received numerous certifications from regulators in Europe, Japan, and Brazil as well as the International Organization for Standardization. Lifecore has also been a leading manufacturer of pharmaceutical-grade, non-animal-sourced hyaluronic acid (HA) since 1981 when we developed our proprietary, fermentation-based HA process. Since then, we have become the preferred viscoelastic supplier to ophthalmic market leaders, and our products have been used in the treatment of more than 100 million patients worldwide. For more information, visit Lifecore Biomedical at **www.lifecore.com.**

Specialized Products & Services

Pfanstiehl is a leading cGMP manufacturer of parenteral-grade excipients and highly potent APIs. Pfanstiehl develops and manufactures high-purity, low endotoxin, low metals carbohydrates, such as Trehalose, Sucrose, Mannitol, Galactose, and Mannose, and Amino acids, such as Arginine, Histidine, Glutamine, and Methionine, along with Sodium Succinate and Sodium Gluconate utilized as injectable excipients for the stabilization of proteins, mAbs, and vaccines. These HPLEs are also used as supplements for cell culture, cell therapy, and cryopreservation media. Being in business for 104 years, Pfanstiehl is well-positioned to exceed the evolving needs of the industry and to help biopharmaceutical and vaccine manufacturers produce safe, effective, and high-quality products. Manufacturing & Development occur at Pfanstiehl's Waukegan campus near Chicago, IL. For more information, visit Pfanstiehl at **www.pfanstiehl.com.**

Global Data & Analytics

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

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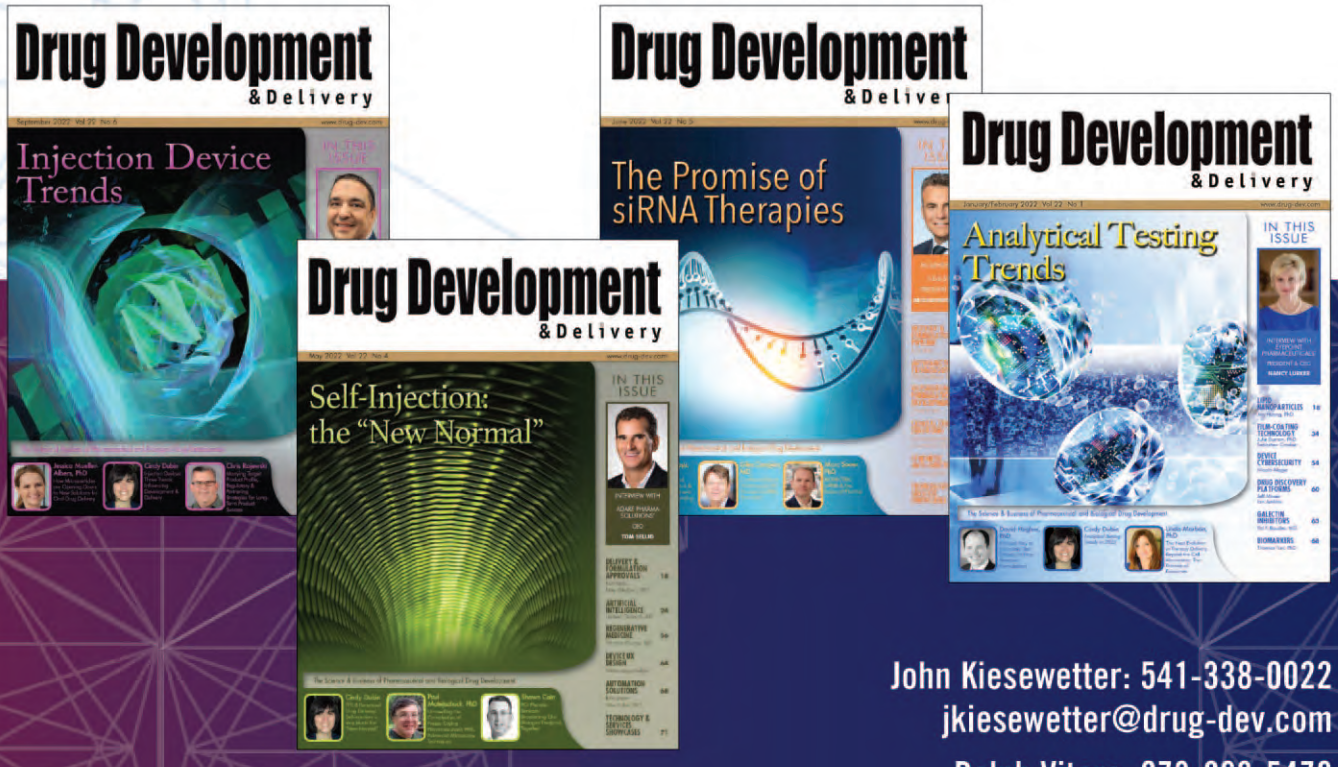

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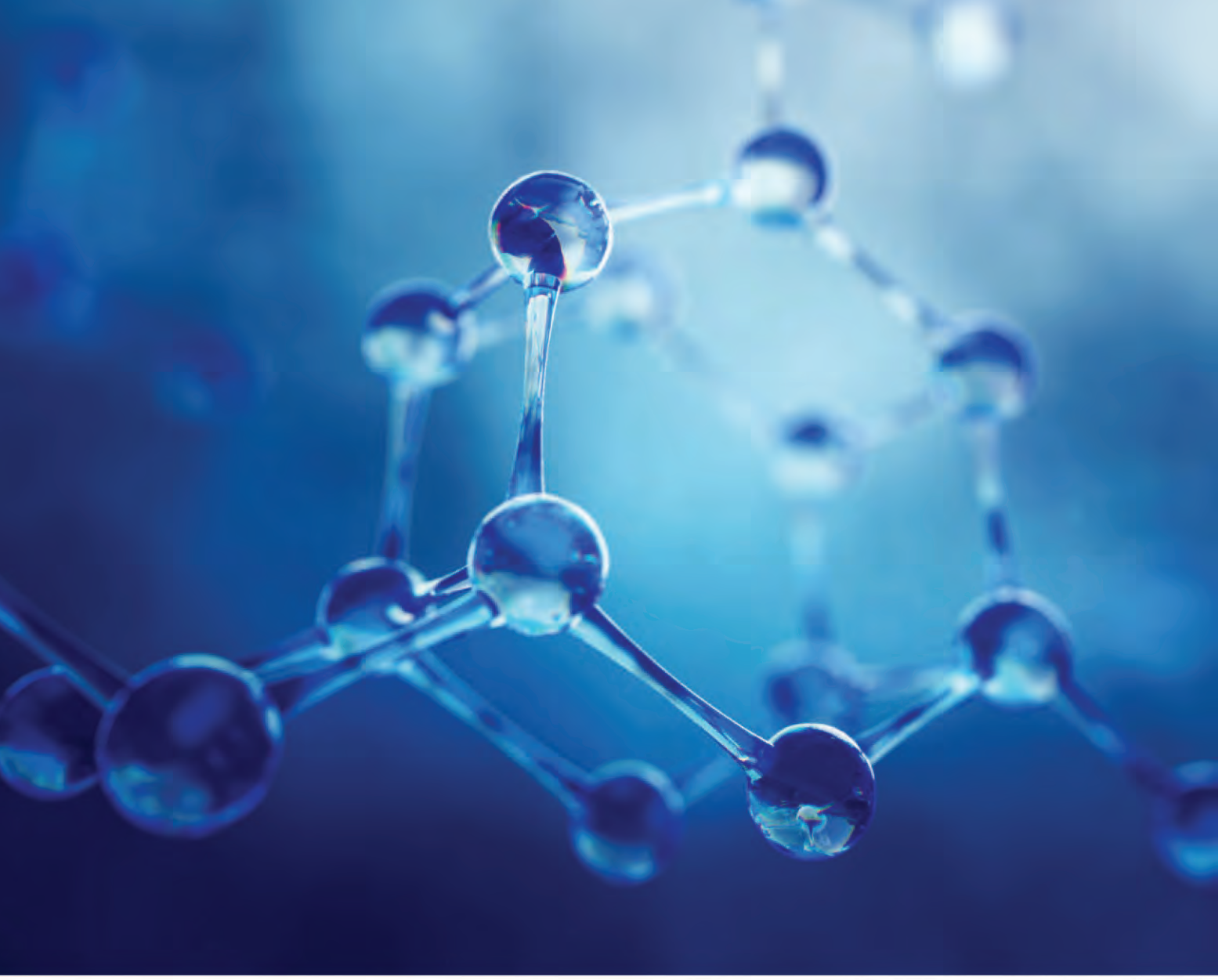

your small molecule has so much potential. our passion for development will help unlock it.

As your trusted CDMO partner offering integrated solutions, Catalent specializes in comprehensive early phase drug development and analytical solutions to get your small molecule drug candidate to clinic fast. Using our rigorous, data-driven scientific expertise, API sparing techniques, and advanced bioavailability enhancement technologies, Catalent can help to identify the right formulation pathway, address complex challenges, and accelerate your drug development journey.

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