Drug Development & Delivery

October 2023 Vol 23 No 7

www.drug-dev.com

Treating Neuropathic Pain Syndromes

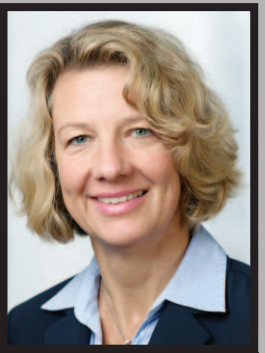
The Science & Business of Pharmaceutical and Biological Drug Development

Charlotte Dunne, PhD
The PTXΔLNP® Platform: On the Promise of Developing New LNPs for Tomorrow's mRNA Therapies

Ronald Aung-Din, MD
Topical NeuroDirect™ Ketamine in the Treatment of Neuropathic Pain Syndromes

James Pipkin, PhD
CAPTISOL® - Part Perseverance & Part Serendipity

IN THIS ISSUE



INTERVIEW WITH

HERMES PHARMA'S

HEAD, STABILITY TESTING & SENIOR QA MANAGER GCP

BERNICE WILD, PHD

CREDENCE MEDSYSTEMS

INNOVATION WITHOUT CHANGE HAS ARRIVED

THE CREDENCE COMPANION

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

This product has not yet been evaluated by FDA

GATTEFOSSÉ

Multifunctional Excipients for your Formulation Needs

- Bioavailability enhancers
- Topical penetration & permeation enhancers
- Sustained release agents
- Suppository and pessary bases
- And more...

Find out how we incorporate our multifunctional excipient know-how with your challenging APIs to address formulation needs

Contact Gattefossé's formulation experts to get started!

info@gattefossecorp.com

www.gattefosse.com

People make our name

Drug Development & Delivery

October 2023 Vol 23 No 7

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

UniSafe® Platform

Delivering the future with safety and simplicity

Developed around UniSafe®, our platform meets the needs of you, our partner, and your varying patients' needs both now and in the future.

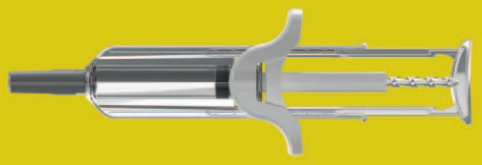
UniSafe® 1mL

A spring-free, passive safety device for 1mL pre-filled syringes, designed for simple assembly and use.

Proven, on market, in patient use

UniSafe® 2.25mL

A spring-free, passive safety device for 2.25mL pre-filled syringes, designed for simple assembly and use.



Fully industrialised and ready to supply

UniSafe® 1mL
Auto-injector

A reusable companion auto-injector for UniSafe® 1mL.

Coming soon

UniSafe® 1mL
Connected Auto-injector

A reusable connected companion auto-injector for UniSafe® 1mL.

Coming soon

Want to know more?

Visit **ompharmaservices.com/ddd-oct2023** or email **pharmaservices@owenmumford.com**

OWEN MUMFORD
Pharmaceutical Services

OMPS/dd&d/ad/ob/1023/7

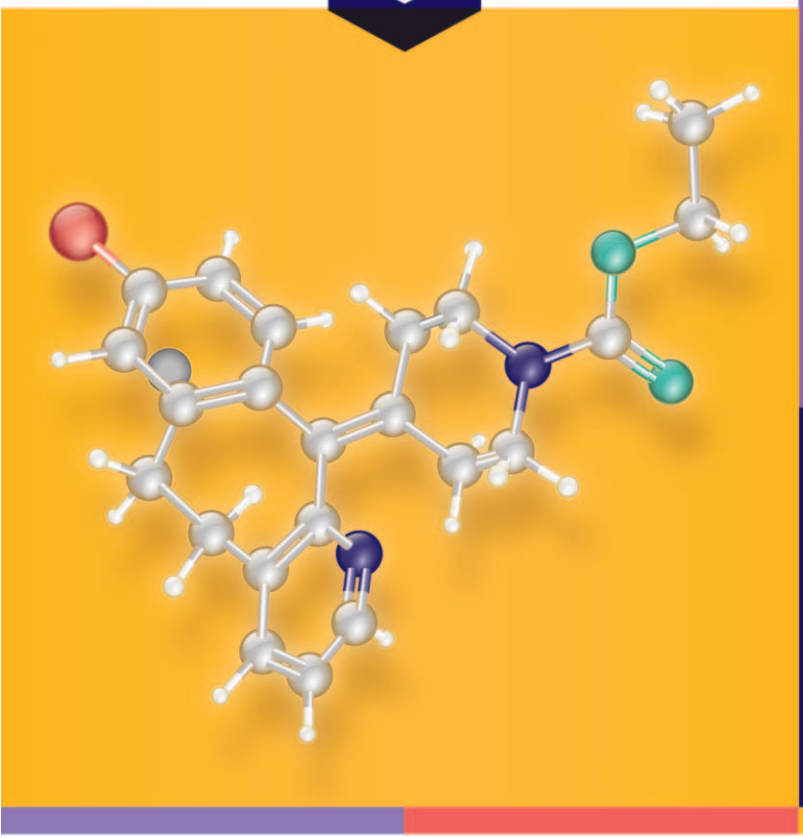
Treating Neuropathic Pain Syndromes

"It is apparent ketamine can play an important role in treating intractable symptoms of neuropathic pain and PTSD. But limiting use is expense, inconvenience, potential side effects, and impracticality as maintenance therapy. We reported previously on the efficacy and convenience of at-home treatment NeuroDirect topical ketamine cream in alleviating persistent symptoms of PTSD and intractable depression. We now report its efficacy in treating a wide variety of neuropathic pain conditions."

p.59

Table of Contents

DO YOU NEED A CDMO THAT CAN DEVELOP THIS



INTO A DRUG LIKE THIS IN RECORD TIME?

EARLY STAGE DEVELOPMENT. ADARE ACCELERATES IT. FIND OUT HOW.

Get to the clinic faster with Adare. We offer comprehensive development services, from preformulation to scale-up, that build a solid foundation for successful proof-of-concept studies. We're experts in developing oral dose formulations for tablets, capsules, suspensions, and minitabs, and we can provide pediatric, modified release, taste masked, and patient-centric formulations. With integrated end-to-end CDMO services that ensure a seamless transition to manufacturing, Adare is with you from start to finish.

Visit us at CPHI Worldwide | Stand #3N30

ADARE®
PHARMA SOLUTIONS

TRANSFORMING DRUG DELIVERY. TRANSFORMING LIVES.

ADAREPHARMASOLUTIONS.COM

Table of Contents

Departments

Primary Packaging Innovation

"In this context, the choice of primary packaging components is crucial. Together, all elements must harmoniously contribute to safeguarding the drug product in dried form during manufacturing, transportation, and storage. The elastomer stopper, which fulfills the role of sealing the vial's contents against the external environment, demands particular attention."

p.51

ASCENDIA PHARMA

Start your project within weeks; not months.

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

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

Technical Services from Ascendia:

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

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

ASCENDIA PHARMA

732-658-4267

bd@ascendiapharma.com

www.ascendiapharma.com

MilliporeSigma to Become First Provider to Offer Fully Integrated mRNA Services

MilliporeSigma, the US and Canada Life Science business of Merck KGaA, Darmstadt, Germany, is the first CTDMO (contract testing, development and manufacturing organization) to offer integrated services for all critical stages of mRNA development, manufacturing, and commercialization, including products and testing. The company recently opened two new GMP-grade mRNA drug substance manufacturing sites in Darmstadt and Hamburg, Germany.

"mRNA has emerged as the breakthrough technology of this century, providing great promise to not only treat, but potentially cure, a wide array of diseases such as cancer, heart disease, and muscular dystrophy," said Dirk Lange, Head of Life Science Services, Life Science business sector of Merck KGaA, Darmstadt, Germany. "We are now the first CTDMO to streamline the entire mRNA process for our clients."

The new sites are part of the company's ongoing € 1-billion investment to advance mRNA technologies and build its global mRNA network and capabilities, as well as through acquisitions, such as AmpTec and Exelead. The € 28- million investment into the new GMP mRNA drug substance manufacturing sites at Darmstadt and Hamburg adds a total of 75 new jobs, providing clients mRNA services at all scales and applications from pre-clinical to commercial. This includes analytical development and biosafety testing specifically designed for mRNA technologies. MilliporeSigma also offers differentiated PCR-based technology for clinical and commercial mRNA manufacturing, providing clients with high-quality mRNA. With this integrated offering, the company can significantly decrease complexities through streamlined and harmonized processes and enhance clients' speed-to-market.

Since the 1990s, the Life Science business of Merck KGaA, Darmstadt, Germany, has collaborated with researchers to ensure they have the critical components and raw materials needed to explore mRNA's potential. Its unique combination of mRNA expertise, technologies, regulatory knowledge, and product portfolios streamlines mRNA manufacturing and testing. The company's mRNA, custom and portfolio lipids, LNP and fill/finish CTDMO services are offered throughout its global network of sites in Schaffhausen, Switzerland; Indianapolis, IN, and Darmstadt and Hamburg, Germany.

The company's Millipore CTDMO Services also provide preclinical through commercial capabilities for monoclonal antibodies and recombinant proteins (mAb and r-proteins), viral vectors (VV), small molecules and high-potent active pharmaceutical ingredients (HPAPI), antibody-drug conjugates (ADCs) as well as integrated analytical development, biosafety testing, and product characterization.

Millipore CTDMO Services are part of the Life Science Services business unit, which together with the Process Solutions business is one of Merck KGaA, Darmstadt, Germany's "Big 3" growth drivers. Merck KGaA, Darmstadt, Germany aims to increase its Group sales to approximately € 25 billion by 2025. Around 80% of the planned sales growth is to come from the "Big 3" growth drivers.

SOHM Announces Acquisition of ABBIE, a World-Class Gene-Editing Platform That Can Deliver Genetic Payloads Using Non-Viral Vectors

SOHM, Inc. recently announced it has acquired ABBIE, a world-class gene-editing platform that can deliver genetic payloads using non-viral vectors. With this acquisition, SOHM is well-positioned as a competitive player in the $5.3- billion gene-editing market in 2023. The gene-editing market is expected to grow to $10.8 billion by 2028 at a 15% CAGR. (Source: 2023, Marketsandmarkets.com.)

ABBIE uses targeted integration to insert larger DNA sequences (aka, genetic payload), including full genes, into a desired loci of the target cell's genome. ABBIE will be able to edit genes of a large number of cell types at different stages of their life cycles, overcoming the limitations of current cell editing and cell engineering technologies.

ABBIE is currently undergoing further development to optimize expression and purification of its protein-based platform. Upon completion of development, ABBIE will become high-quality, off-the-shelf cell engineering kits. Gene-editing companies will use ABBIE kits to deliver a gene payload to a specific locus on their targeted cells.

Revenue generations can be obtained immediately through licensing and gene-editing kits slated to be released for commercialization in 3Q/4Q 2024. ABBIE is expected to reach in-human trial on or before 4Q 2025. The global biotechnology kit market is estimated at $593 billion in 2022 and projected to grow at a 10.9% CAGR between 2023 and 2030. (Source: 2023, GrandViewResearch.com.)

ABBIE's development is being led by David Aguilar PhD, SOHM's COO. Dr. Aguilar has extensive experience in molecular and cellular biology, genome editing, and has been an entrepreneur in biotechnology since 2015.

"ABBIE is a platform tool that delivers genes of interest for clinical trials. Compared to other gene-editing technologies, ABBIE has achieved the same level of progress with much less R&D spending. Our strategic partnerships and capital management have enabled us to streamline development and expedite our commercialization," said Dr. Aguilar.

ABBIE was acquired from CGA 369 for $10 million. The first payment of $6 million will be paid in 12 months from the effective date and will be a combination of $3 million cash and $3 million in restricted common stock. The remaining $4 million payment to CGA 369 will be triggered by ABBIE's first $50 million of commercial sales.

CGA 369 is a cutting-edge bio tech company revolutionizing the way proteins are expressed, validated and engineered, paving the way for a future of endless possibilities. CGA 369 caters to the emerging cell engineering space by specializing in protein expression, offering state-of-the-art technologies and innovative solutions to harness the full potential of proteins. The company is driven by a dedicated team of experts combining expertise in molecular biology, genetic engineering and bioinformatics to unlock the intricate mechanisms of protein synthesis, ensuring precise and optimized expression for a wide range of applications.

Bora Collaborates With Sunway Biotech to Launch Global Nutraceuticals Offering

Bora Health, a global design, development, and distribution partner of pharmaceuticals and health foods and part of the Bora group, recently announced its collaboration with Sunway Biotech, a leading ingredients manufacturer, and research and development (R&D) organization. Resulting in the parent company of Bora Health, Bora Pharmaceuticals becoming the largest shareholder of Sunway Biotech.

Sunway Biotech gives the Bora Group access to a full suite of fermentation and extraction facilities with full R&D and analytical capabilities. Bora's CDMO business will be able to use Sunway's yeast manufacturing technology at its facility in Taipei, Taiwan to produce Ankascin 568-R, an ingredient used for the formulation of dietary supplements and fortified foods for its customers across the world.

Ankascin 568-R is extracted from fermented products of patented functional red yeast strain (Monascus purpureus NTU 568). It is the only FDA approved red yeast ingredient available on the US market without the controversial ingredient monacolin K (Lovastatin). Ankascin 568-R helps support blood glucose management, cardiovascular health, memory, cognitive health, and healthy ageing.

Bobby Sheng, CEO of Bora Group, said "The global nutraceuticals market is expected to grow at a compound annual growth rate (CAGR) of 9.4% by 2030. This growth is fueled by consumers increasingly turning to nutraceuticals for their proven health benefits. We're thrilled to now have the controlling interest in Sunway Biotech giving us access to technology that manufactures Ankascin 568-R and Vigiis101-LAB. As we continue to grow our service range as a CDMO, we are excited to be entering the supplements market. With Sunway's fermentation know-how, not only will we have a unique patented ingredient in Ankascin 568-R, we will also be able to create products for the growing prebiotic, probiotic, and postbiotic market."

Vigiis101-LAB is a probiotic that contains a patented functional strain called Lactobacillus paracasei subsp. paracasei NTU 101 that is legally consumable in the EU, China, Taiwan, and Canada. It's suitable for the formulation of dietary supplements and fortified foods and used for enhancing digestion and improving gastrointestinal microbiota.

Sheng continued "Simon Chang will act as Vice Chairman of Sunway and CEO, John Pan will continue to lead operations for Sunway Biotech. As one of Bora's more senior leaders, it's great to have Simon lead us into this buoyant market."

Founded in 2007, Sunway Biotech was established as a center of excellence for the research and development of health food and ingredients. The organization was awarded the GOLD award at Taiwan's BIO awards in 2022 and the Ankascin 568-R has been shortlisted in the Botanical category at the Nutraingredient USA Awards 2023.

Bora Group is a trusted outsourcing partner to some of the largest pharmaceutical companies across the globe. It offers a significant portfolio of expertise and industry experience in pharmaceutical, healthcare and nutraceutical products across the entire pharmaceutical supply chain from research and development, to sales and distribution.

LIXTE Biotechnology Announces a Supported Collaborative Trial to Study LIXTE's First-in-Class PP2A Inhibitor, Plus GSK's Immunotherapy in Clear-Cell Ovarian Cancer

LIXTE Biotechnology Holdings, Inc. recently announced a Phase 1b collaborative clinical trial to assess whether adding Lixte's LB-100 to GSK's programmed death receptor-1 (PD-1)-blocking monoclonal antibody, dostarlimab, may enhance the effectiveness of immunotherapy in the treatment of ovarian clear cell carcinoma (OCCC). The clinical trial is sponsored by The University of Texas – MD Anderson Cancer Center and will be conducted at MD Anderson and will also be open at Northwestern University's Robert H. Lurie Comprehensive Cancer Center. LIXTE will provide LB-100; GSK will provide dostarlimab and financial support for the clinical trial.

The clinical trial is based on the observation of longer survival of patients with OCCC treated with immunotherapy whose cancer cells have an acquired gene mutation resulting in a reduction in PP2A. This finding was reported by the lead clinical investigators of this new trial: Amir Jazaeri MD, Professor of Gynecologic Oncology at MD Anderson, and Emily Hinchcliff, MD, MPH, Assistant Professor of Obstetrics and Gynecology at Northwestern University Feinberg School of Medicine. The observation by Drs. Jazaeri and Hinchcliff, that a genetically acquired reduction in PP2A enhances sensitivity to immunotherapy, raises the possibility that reducing PP2A pharmacologically with LB-100 will enhance the anti-tumor effect of the PD-1 blocking monoclonal antibody dostarlimab in patients with OCCC lacking the genetic reduction in PP2A.

John S. Kovach, M.D., LIXTE's founder and Chief Executive Officer, said "Preclinical data supports the idea that LB-100 enhances the efficacy of PD-1 therapy. Clinical data also supports this idea, in that patients with ovarian clear cell carcinoma with dysfunctional PP2A due to somatic mutations in PPP2R1A have shown dramatically longer survival after treatment with immune checkpoint blockers."

Dr. Hinchcliff added "OCCC is a comparatively chemotherapy resistant disease and therefore has very limited options for treatment. This clinical trial is an exciting alternative approach that leverages the potential synergy between these two agents and is aiming to improve the impact immunotherapy may have for these patients."

LIXTE Biotechnology Holdings, Inc. is a clinical-stage pharmaceutical company focused on new targets for cancer drug development and 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.

Samsung Biologics Announces Expanded Strategic Agreement With Bristol Myers Squibb

Samsung Biologics recently announced a new agreement with Bristol Myers Squibb for large-scale manufacturing of a Bristol Myers Squibb commercial antibody cancer drug substance.

Bristol Myers Squibb and Samsung Biologics have an existing manufacturing agreement for a commercial antibody cancer drug and have expanded the strategic relationship over time. Under the terms of the new agreement, Samsung Biologics will provide drug substance manufacturing for an antibody cancer drug substance at the company's latest and largest biomanufacturing facility, Plant 4, in Songdo, South Korea.

"Our relationship with Bristol Myers Squibb spans over a decade, and we are proud and excited to help bring important medicines to patients around the world," said John Rim, President and CEO of Samsung Biologics. "This collaboration with Bristol Myers Squibb underscores our commitment to expediting the delivery and ensuring the continuous supply of client pipelines, enabled by our commitment to manufacturing quality, innovation, and capacity."

Samsung Biologics is a fully integrated, end-to-end CDMO service provider, offering seamless development and manufacturing solutions from cell line development to final aseptic fill/finish as well as laboratory testing support for the biopharmaceutical products we manufacture. Our state-of-the-art facilities are cGMP compliant with bioreactors ranging from small to large scales to serve varying client needs. To maximize our operational efficiency and expand our capabilities in response to growing biomanufacturing demands, Samsung Biologics fully completed Plant 4, which will further advance the company's standing as the world's largest manufacturing facility at a single site—holding a 604KL total capacity—and announced plans to construct Plant 5, which will be operational in April 2025. Additionally, Samsung Biologics America enables the company to work in closer proximity to clients based in the U.S. and Europe.

We continue to expand our capabilities to accommodate our clients by investing in technologies such as an antibody-drug conjugate (ADC) facility, a dedicated mRNA manufacturing facility, and additional aseptic filling capacity. As a sustainable CDMO partner of choice, we are committed to on-time, in-full delivery of the products with our flexible development and manufacturing solutions, operational excellence, and proven expertise.

"With 80 years of combined experience working with Captisol and other cyclodextrins, our team is ready for any formulation challenge and look forward to helping you bring your product to market." — Lian Rajewski, PhD, Sr. Research Investigator

Your Partner in Solubility.

The scientists at Ligand Pharmaceuticals are experts at working with Captisol, have developed products in-house and aided clients in developing many successful formulations. Our expertise in navigating CMC, regulatory, and clinical issues is unparalleled in the industry. Captisol is a solubility enhancing excipient (derivatized cyclodextrin) that has been on the market for over 20 years and is in more than a dozen approved products.

Our Team is Ready. Are you? Contact us today!

858.550.5632 | cdinfo@captisol.com | Captisol.com

2033 Becker Drive | Suite 310 | Lawrence, KS 66047

Biora Therapeutics Announces Submission of IND Application for BT-600 Program Featuring NaviCap Ingestible Drug Delivery Device

Biora Therapeutics, Inc. recently announced submission of an Investigational New Drug (IND) application with the US FDA that supports the next phase of development of BT-600, a drug/device combination designed to use Biora's NaviCap ingestible drug delivery device with a proprietary liquid formulation of tofacitinib, for the treatment of moderate-to-severe ulcerative colitis.

"Today's announcement is an important milestone for Biora Therapeutics. The IND application leverages clinical device function study data from four separate studies in both healthy volunteers and patients with active ulcerative colitis, with more than 40 study participants receiving over 80 NaviCap devices," said Ariella Kelman, MD, Chief Medical Officer of Biora Therapeutics. "We look forward to initiating our Phase 1 study in the US this year and advancing this technology, which we believe could lead to better patient outcomes in ulcerative colitis."

The IND application for BT-600 includes extensive manufacturing, preclinical, human device function, and toxicology data to support a first-in-human clinical trial for BT-600. The Phase 1 trial of BT-600 is expected to be a randomized, double-blind, placebo-controlled study to evaluate safety, pharmacokinetics and pharmacodynamics, including effects on colon tissue, in healthy volunteers receiving the NaviCap device filled with a novel liquid formulation of tofacitinib at 5-mg and 10-mg doses. The NaviCap device has been designed for targeted delivery directly to the colon in this application.

The FDA will review the application and determine the acceptability of the data before Biora begins its first clinical trial for BT-600. It is possible that the FDA will require additional information.

Biora's NaviCap targeted oral therapeutics platform utilizes a novel approach that could improve patient outcomes by enabling delivery of therapeutics directly to the site of disease, increasing therapeutic levels in tissue while reducing systemic uptake. For the 1.8 million patients in the US who suffer from inflammatory bowel disease (IBD), existing therapeutics offer less than ideal efficacy, likely because of the challenges with safely achieving sufficient drug levels in the affected tissues. Research has shown that targeted delivery of therapeutics has the potential to improve patient outcomes in IBD.

The NaviCap platform uses an ingestible device designed for targeted delivery of therapeutics to improve treatment of IBD. Once swallowed, Biora's GItrac autolocation technology enables the device to autonomously identify targeted locations in the GI tract and release a therapeutic dose of up to 500 μl.

Biora's BT-600 program consists of a unique, liquid formulation of tofacitinib delivered to the colon via the NaviCap device, for the treatment of ulcerative colitis. Studies in healthy volunteers have demonstrated accurate localization and delivery in a fasted state and demonstrated the device's ability to function in both fasted and fed states, making it potentially the first ingestible therapeutic delivery device that does not require fasting or other food restriction for use. A device function study in participants with active ulcerative colitis (UC) also demonstrated successful device performance in active UC patients. The company submitted an IND application to begin a Phase 1 study for its BT-600 program in September, 2023.

New Collaboration With Stevanato Group to Elevate mRNA Production With Nfinity Platform

Quantoom Biosciences recently announced a new collaboration with Stevanato Group, a leading global provider of drug containment and delivery solutions to the pharmaceutical, biotechnology, and life science industries, with the goal of promoting and democratizing access to cutting-edge mRNA production technologies worldwide. The focus of this collaboration lies in harnessing the potential of Quantoom's revolutionary Nfinity Platform, a state-of-the-art, fully automated mRNA production platform, to contribute to the betterment of global health. This collaboration brings together the innovative capabilities of both industry leaders with a shared vision to enhance global health outcomes through advanced engineering and scientific solutions.

The Nfinity Platform comprises multiple systems, designed with a small footprint, seamless automation, and cost-effectiveness. Tailored to cater to the burgeoning demand for DNA and mRNA manufacturing and encapsulation, these systems are synergistically integrated with custom single-use consumables and ready-to-use reagent premixes. By combining their respective expertise, Quantoom and Stevanato Group will strive to cultivate a scalable optimized technology portfolio that would enable the economical production of mRNA on a global scale, thereby advancing the treatment landscape and improving global health.

"Our journey began less than 2 years ago with a vision to revolutionize mRNA production, and today, I am immensely proud of the strides we've made. The collaborative efforts poured into our Nfinity Platform have yielded an exceptional automated mRNA production solution. The vitality of this collaboration with Stevanato Group underscores the innovative spirit that drives us. Witnessing where the company stands today is not only exciting but a testament to the dedication and ingenuity of our team, as well as the meaningful partnerships we forge," said José Castillo, Chief Executive Officer at Quantoom Biosciences.

"Stevanato Group has the potential to bring innovation to the mRNA field," said Andrea Zambon, Corporate Business Development Director at Stevanato Group. "Our expertise and capabilities in primary packaging, equipment, and analytical services for biopharmaceutical manufacturing make Stevanato Group the natural partner for Quantoom. Together, our companies can enable customers to introduce new mRNA-based drugs into the market faster, benefiting the patients waiting for them."

ENVISION YOUR IMPACT

Try the Aclar® Impact Estimator tool today!

Aclar® film delivers the highest moisture barrier, while significantly reducing pack size, waste and carbon emissions, when compared to the same product packaged in Cold Form Foil (CFF).

By using our new **Aclar Impact Estimator** tool, find out:

- The number of shipping containers of packaging material that can be saved annually
- Reduction in transportation-related CO_2 emissions

This tool will give you a high level, unique view around the waste reduction that can be achieved by using Aclar®

Scan to Learn More

THE FUTURE IS WHAT WE MAKE IT

Honeywell

Rhythm Pharmaceuticals Receives Orphan Drug Designation for Setmelanotide for Treatment of Acquired Hypothalamic Obesity

Rhythm Pharmaceuticals, Inc. recently announced the European Medicines Agency (EMA) has issued a positive opinion on the company's orphan drug designation request for setmelanotide as a treatment for acquired hypothalamic obesity.

"Acquired hypothalamic obesity is a serious disease with severe implications for patients and families and no effective treatment options," said Yann Mazabraud, Executive Vice President and Head of International at Rhythm. "We are pleased with this EMA positive opinion as it underscores the significant unmet need for these patients and the potential of setmelanotide to bring a precision medicine approach that may benefit patients with this disease across Europe."

EMA orphan drug designation is granted to drugs intended for the treatment, diagnosis, or prevention of life-threatening or chronically debilitating conditions affecting no more than five in 10,000 individuals in the European Union.

Rhythm is evaluating setmelanotide in a global Phase 3 clinical trial in acquired hypothalamic obesity and expects to complete patient enrollment in the fourth quarter of 2023.

Acquired hypothalamic obesity is a rare form of extreme obesity that occurs following damage to the hypothalamic region of the brain, which includes the MC4R pathway and is responsible for controlling physiological functions such as hunger and weight regulation. It most frequently follows the growth or surgical removal of craniopharyngioma, astrocytoma, or other rare brain tumors. Patients experience rapid weight gain, a reduction in energy expenditure, and an increase in hunger leading to severe obesity within six to 12 months following tumor resection. Rhythm estimates there are approximately 3,500 to 10,000 patients living with acquired hypothalamic obesity in the European countries of Germany, France, Spain, Italy, The Netherlands, and the United Kingdom.

Rhythm is a commercial-stage biopharmaceutical company committed to transforming the lives of patients and their families living with hyperphagia and severe obesity caused by rare melanocortin-4 receptor (MC4R) diseases. Rhythm's lead asset, IMCIVREE (setmelanotide) is approved by the US FDA and authorized by the European Commission (EC) and the UK's Medicines & Healthcare Products Regulatory Agency (MHRA) for use in accordance with product labeling.

Additionally, Rhythm is advancing a broad clinical development program for setmelanotide in other rare MC4R pathway diseases, as well as a preclinical suite of investigational candidates for the treatment of congenital hyperinsulinism. Rhythm's headquarters is in Boston, MA.

ALSA Ventures Launches Novel Gene Therapy Portfolio Company Axovia Therapeutics

ALSA Ventures recently announced the acquisition of Axovia Therapeutics Inc and the launch of a new portfolio company Axovia Therapeutics Ltd. Axovia is developing the first gene therapies for ciliopathies and has a pipeline of products for these devastating diseases, including Bardet-Biedl Syndrome (BBS).

The ALSA Ventures' investment team has designed an accelerated development plan to take the lead program AXV101 into clinical trials in the next 18-24 months with a rapid path to clinical proof of concept and approval.

AXV101 is an AAV9-based gene therapy targeting retinal dystrophy associated with BBS in patients carrying biallelic mutations in the BBS1 gene. It is designed to halt retinal degeneration, which begins in childhood leading to blindness before 20 years of age.

Revised epidemiological analyses suggest that BBS affects between 1 in 70,000 – 1 in 100,000 in Europe and North America, and there is no treatment for the retinal degeneration.

ALSA Ventures CEO, Alek Safarian, said they were excited to take AXV101 into clinical trials, which will have access to well-characterised and motivated patients. "Especially pediatric patients who need early treatment before permanent vision damage occurs. Our investment team was particularly attracted to Axovia Therapeutics as a valuable addition to our growing portfolio of companies because of its striking preclinical results, its Rare Pediatric Disease Designation, and the proven AAV delivery mechanism."

The company is well positioned for an FDA priority review voucher (PRV) which is awarded to sponsors that develop drugs for diseases, including rare paediatric diseases. Axovia is based on decades of work on ciliopathies at University College London by co-founders Professor Phil Beales and Dr Victor Hernandez.

Axovia Acting CEO Professor Phil Beales said the Axovia gene therapy platform gives hope to BBS patients worldwide. "In preclinical studies, our BBS1 novel gene therapy modified the underlying disease of BBS, including rescuing vision loss by halting retinal degeneration."

Professor Beales is a renowned scientist and diagnostic leader in ciliopathies, having led research and patient care efforts out of University College London (UCL) Institute of Child Health for one of the most debilitating ciliopathic diseases in the world – BBS.

"Our novel gene therapy utilizes an adeno-associated virus (AAV9) to deliver a functional copy of the faulty BBS gene in key tissues," he said. "Since AAV is not known to cause human disease and can be tightly controlled (it does not replicate like disease-carrying viruses), it has been the gene delivery method of choice for multiple therapies, including Luxturna for retinal disease."

Available clinical data on more than 3,000 people treated over more than 20 years indicate that AAV gene therapy is well-tolerated and efficacious. We are grateful to Fieldfisher LLP for their assistance on the transaction.

pci
PHARMA SERVICES

Your injectable drug product destination.
Our world.

Advanced Drug Delivery

Driven by innovation and patient-centricity, our design and development expertise combined with our device assembly and advanced packaging capabilities offer flexible solutions for a diverse portfolio of conventional and specialty injectable drug delivery devices.

END-TO-END DRUG DEVICE COMBINATION PRODUCT SOLUTIONS:

- Sterile fill-finish of syringes and cartridges for auto-injectors
- Final assembly and labeling of:
  - prefilled syringes
  - auto-injectors
  - pens
  - on-body injectors
- Integrated top-load cartoning
- Serialization
- Cold chain storage

www.pci.com

talkfuture@pci.com

Your bridge between life-changing therapies and patients

Curia Supports Replicate Bioscience's Phase 1 Clinical Trial of Novel Next-Generation RNA Vaccine

Curia recently announced its partner, Replicate Bioscience, has received IND clearance from the FDA and has dosed the first participant with RBI-4000, a self-replicating (srRNA) rabies vaccine, in a Phase 1 clinical study utilizing clinical material developed as part of the collaboration with Curia.

Curia conducted process development, scale-up, and cGMP manufacture of srRNA RBI-4000 drug substance. At approximately 10,000 bases, this srRNA is significantly larger than a conventional linear mRNA and has been historically difficult to manufacture at the scales required for clinical development. Curia's analytical method development and qualification of the assays were also critical to the release of this srRNA molecule.

"Curia is proud to be a pioneer in manufacturing this new class of srRNA technology by delivering RBI-4000 srRNA drug substance to our partner Replicate in support of their Phase 1 clinical trial," said Christopher Conway, President, Research & Development, Curia. "We are dedicated to providing advantaged solutions from development to cGMP manufacture for our customers in the mRNA field."

This new class of srRNA vaccine offers a number of potential improvements to existing mRNA vaccines, including lower dosage requirements and improved tolerability. The advancement also opens the door for further RNA innovation for use in vaccines and therapeutics with fewer constraints on molecule size.

"Our collaboration with Curia helped us manufacture a new class of self-replicating RNAs which have the potential to deliver improved bioactivity, tolerability and efficacy profiles as compared to other RNA technologies," said Nathaniel Wang, PhD, founder and CEO of Replicate. "Curia scaled up a process for longer RNAs that enabled large-scale production at yields, purity and potency to support Replicate's Phase 1 clinical trial."

Curia is committed to being a partner of choice from discovery and development through manufacture and commercialization, providing a full suite of services to support small and large molecule, drug substance, drug product aseptic fill-finish and laboratory testing at every phase of the drug development life cycle.

Curia, formerly AMRI, is a leading contract research, development, and manufacturing organization providing products and services from R&D through commercial manufacturing to pharmaceutical and biopharmaceutical customers. Curia's nearly 4,000 employees at 29 locations across the US, Europe, and Asia help its customers advance from curiosity to cure. For more information, visit CuriaGlobal.com.

POINT Biopharma & Athebio Announce Partnership to Develop Designed Ankyrin Repeat Protein Targeted Radioligands

POINT Biopharma Global Inc. and Athebio AG recently announced a collaboration and license agreement to develop and commercialize DARPin-targeted radioligands (Radio-DARPins). DARPins are an attractive ligand class for cell-surface targets that could enable access to cell "surfaceome" targets beyond catalytic and ligand binding sites typically accessible to small molecules and peptides. DARPins combine the small molecule feature of rapid tumor penetration and clearance from the body, with the antibody-like ability of binding to a wider range of proteins and other cell surface targets. Their well-behaved and customizable formatting options, including stability at high concentrations and temperatures, are expected to facilitate rapid discovery, validation, and commercial scale manufacturing applicable to fast (212Pb) and slower (177Lu, 225Ac) decaying isotopes.

The collaboration gives POINT exclusive access to Athebio's intellectual property and capabilities in DARPin development in the radioligand therapy field. Together, the parties will collaborate in discovery, candidate selection and preclinical development of Athebody DARPins for use as Radio-DARPin drug entities. POINT will be solely responsible for the clinical development and commercialization of Radio-DARPins translated from the discovery collaboration.

"The holy grail of radioligand development is the ability to engineer ligands that can precisely deliver radiation and also have physical properties that are resistant to radiolytic damage, enabling them to be manufactured at scale," said Joe McCann, PhD, Chief Executive Officer of POINT Biopharma. "DARPins represent a potential goldilocks opportunity in this regard, and could unlock new cell surface targets creating a new horizon for the development of novel targeted radioligand therapies. I am excited by this collaboration with Athebio, experts in DARPin technology, as it further expands our library of tools to engineer next-generation radioligands."

"We are very excited to join forces with POINT. POINT is uniquely positioned in the radiotherapy field and just as committed as we are to unlock the full potential of Athebody DARPins to develop radiopharmaceuticals for patients in need," said Patrik Forrer, one of the inventors of the DARPin technology and CEO and Chairman of Athebio. "The exceptional properties of our Athebody DARPins make them ideally suited for targeting radioisotopes. In particular their high stability should allow for simple conjugation to radioisotopes and their small size and high affinity binding with precise specificity should allow for superior targeting of tumors. The convergence of these attributes holds immense promise for pushing the boundaries of radiotherapy."

POINT Biopharma Global Inc. is a globally focused radiopharmaceutical company building a platform for the clinical development and commercialization of radioligands that fight cancer. POINT aims to transform precision oncology by combining a portfolio of targeted radioligand assets, a seasoned management team, an industry-leading pipeline, in-house manufacturing capabilities, and secured supply for medical isotopes including actinium-225 and lutetium-177.

ATHEBIO enables its partners to develop superior targeted therapeutics of advanced efficacy and safety and thereby increased probability of clinical success. ATHEBIO's proprietary "plug & play" Athebody platform is based on clinically validated designed ankyrin repeat proteins (DARPins) and can unlock therapeutic options not easily accessible with current antibody technologies. Rather than building up its own pipeline, ATHEBIO licenses tailor-made Athebody DARPins to its partners.

CEOLUS™
Just Pure Performance

AsahiKASEI

Make The Smart Choice

Asahi Kasei microcrystalline cellulose (MCC) Ceolus™ brings a key difference compared with standard MCC products: its high performance stemming from innovative particle morphology.

Why is Ceolus™ **The Smart Choice** for you?

Solutions made possible by Ceolus™

Enables challenging formulations
e.g., Poorly compactible APIs, high dose APIs, poorly flowable APIs

Solves tableting issues
e.g., Insufficient hardness, capping, insufficient API content uniformity

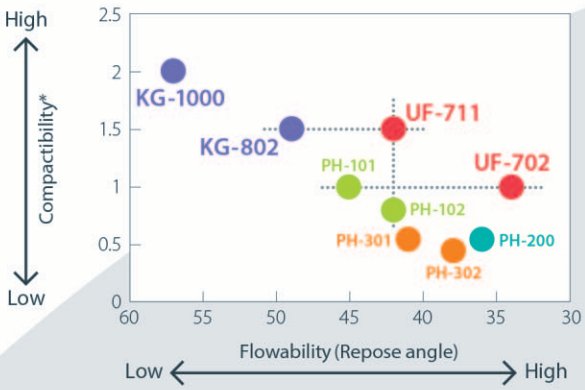
Enables unique and patient-friendly dosage forms
e.g., MUPS, multiple-API-combination tablets, small tablets

Improves the quality of formulations
e.g., Low nitrosamine-associated risk, less black particles, high-quality consistency

Grade lineup

Ceolus™ KG Highly compactible MCC with fibrous particles	KG-1000 KG-802
Ceolus™ UF Porous MCC with balance of compactibility and flowability	UF-702 UF-711
Ceolus™ PH Standard grade with high quality	PH-101, 102 PH-200 PH-301, 302

Map of Ceolus™ Compactibility vs. Flowability



* Comparison of tablet hardness, with the formulation of PH-101 = 1 set as the index point
Formulation: Acetaminophen/MCC = 70/30

Inquiries

ASAHI KASEI CORPORATION

E-mail: ceolus_2@om.asahi-kasei.co.jp

www.ceolus.com/en/

Formulation Forum

CUBOSOMES – The Next Generation of Lipid Nanoparticles for Drug Delivery

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

Jim Huang, PhD
j.huang@ascendiapharma.com

Shaukat Ali, PhD
shaukat.ali@ascendiapharma.com

INTRODUCTION

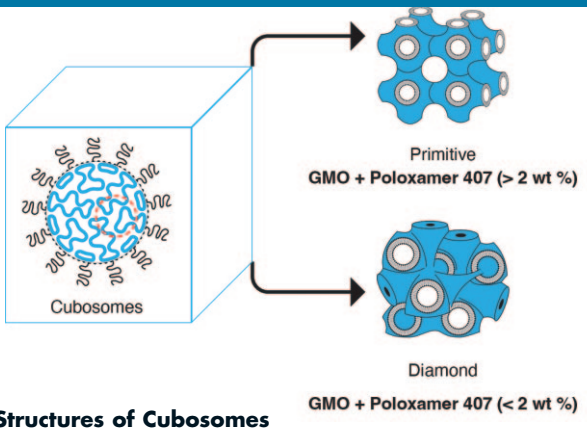
Cubosomes are lipid-based highly stable nanoparticles.[1] They are soft structured membrane assemblies of lipid bi-continuous cubic liquid crystalline phases with interior water channels stabilized by polymeric outer corona surfaces. These mesomorphic cubic phases are composed of unique low-melting lipids with a single bilayer bearing continuous membrane lattice structure with pores leading to water channels.[2] With the invent of modern new characterization techniques, such as small-angle x-ray scattering, for instance, it has shed light into microstructures and mechanisms of drug delivery of these LNPs. With unique structures, cubosomes provide a significantly higher surface area for their greater abilities to solubilize hydrophobic and hydrophilic molecules with relatively higher loading as opposed to liposomes. These lipid nanoparticles, or cubosomes, can be engineered with highly selective lipid components to deliver a wide range of molecules.[3]

Ascendia Pharma recently introduced LipidSol®, a lipid-based platform technology for the delivery of small molecules with poor solubility, peptides, gene therapy, and biologics in lipid nanoparticles.[4] One of the assemblies could adapt the bi-continuous cubic phases (or cubosomes) depending upon lipid composition and type, which markedly differ from traditional liposomes, in which the outer surfaces are stabilized by polymers or co-polymers with PEG moieties. Cubosomes possess an ability to tune the membrane curvature with larger surface areas independently as opposed to bilayer membranes. In addition, the hydrophobic volume fraction of a monoolein cubosomes is about 100 nm in diameter, which is typically around three times larger than a small unilamellar vesicle (SUV) with similar size.[5] As we continue to explore the LipidSol-enabling technologies in drug delivery, the following will shed light on the design and formation of cubosomes with special focus on their applications for delivery of hydrophobic and hydrophilic small and large molecules, including oncology drugs and polynucleotides (DNA, mRNA, and siRNA).

STRUCTURE OF CUBOSOMES

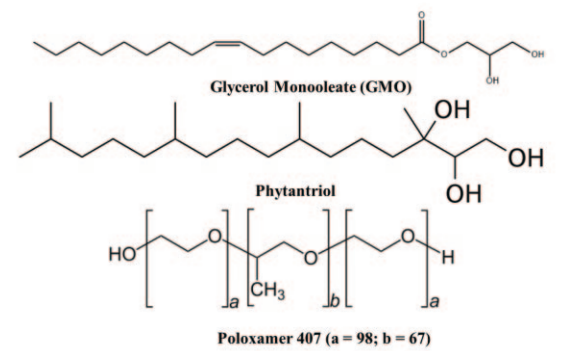
Cubosomes are categorized into two morphological structures, namely primitive cubosomes and diamond based on lipid compositions and types (Figure 1).[6] Cubosomes are composed of amphiphilic low-

FIGURE 1



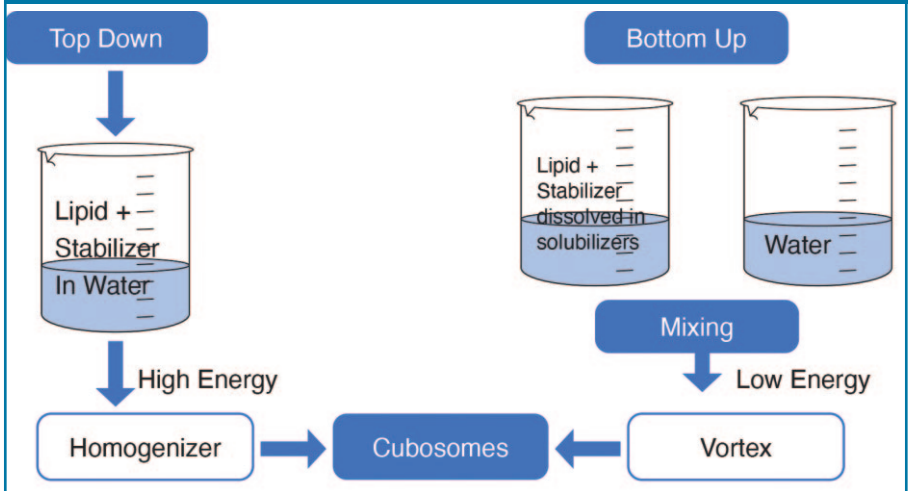
Structures of Cubosomes

FIGURE 2



Structures of Lipids & Surfactant

FIGURE 3



Preparation of Cubosomes

melting monoolein (a monoglyceride) and/or phytantriol and stabilized by polymeric solubilizers/surfactants. As shown in Figure 1, the lipids are typically monoolein or phytantriol, and poloxamer 407 is used as a stabilizer. Their chemical structurers are shown in Figure 2.

Upon hydration with water, these lipids spontaneously form cubic liquid crystalline phases arranged in primitive or double diamond assemblies with the phase transition between 43°C and 80°C. The stabilizers inevitably play a crucial role in providing longer stability, controlling the phase boundaries and drug release through the restrictive water channels.

PREPARATION & CHARACTERIZATION OF CUBOSOMES

Cubosomes are prepared by the top down (high shear energy) or bottom up (low shear energy) approach as outlined in Figure 3.

It requires the dispersion of lipids in aqueous solution followed by sonication or low-shear mixing or high-shear homogenization. If using organic solvents as hydrotropes, following evaporation, the dried film is hydrated with buffer or saline and sonicated, which results in formation of cubosomes.[7] If heating is controlled, there is a lesser chance of degradation of lipids and formation of homogeneous dispersions. To alleviate the rise in temperature during sonication, a temperature-controlled cup horn system is utilized as an alternative to sonicator tip. Spicer, et al investigated stable monoolein-derived cubosomes with lower polydispersity via sonication of an aqueous solution containing ethanol as a hydrotrope.[8] This process can further be optimized using propylene glycol and polyglycerol ester to avoid any inherent residual solvents like ethanol for delivery of proteins and vaccines as described by Rizwan, et al.[9] Other methods, such as microfluidics, are also applied to further offset the heating issues and enhance the production at much larger scale.[10]

DSC, NMR, and fluorescence spectroscopy techniques have been used for characterization of lipid vesicle morphologies and bilayer structures, but a high-energy small angle x-ray scattering (SAXRD) method is commonly used to identify the cubosomes.[2] The characteristic diffraction patterns in SAXRD from the fingerprints and spacing in between the rings identifies the certain morphology of the lipid packing to determine the packing of these lipids. Furthermore, cryo-transmission electron microscopy (Cryo-TEM) is also an excellent technique for characterization of the lipids in the cubosomes. Cubosomes, for example, designed with glycerol monooleate, polyglycerol ester, and poloxamer 407 show the continuous structures with vesicle formation at the surface with water channel surrounding the exterior. Dynamic light scattering (DLS) is used to measure the particle size distribution and polydispersity.

APPLICATION OF CUBOSOMES

Large Molecules

Cubosomes can encapsulate small and large molecules, including proteins. Tabel 1 shows the encapsulation of proteins and

TABLE 1

Protein/MW	Formulation	Observation
Cholera toxin B subunit/12 kDa	Phytantriol, glycolipid monosialoganglioside GM1, Poloxamer 407	Specific binding of cholera toxin B, cubosomes could be used for biosensing probes
Nerve growth factor/13.5 kDa	Monoolein, bet casein stabilizer	Enhancing bioavailability of drug in guinea pigs
Beta Casein/24 kDa	Monoolein or phytantriol & Poloxamer 407	Beta casein acts as co-stabilizer and forms hexagonal phase
Ovalbumin/44.3 kDa	Monoolein or phytantriol & Poloxamer 407	Encapsulation of ovalbumin for sustained-release profile
siRNA/19 base pairs	Monoolein, DOTAP	Specific gene silencing with improved endosome escape
siRNA/22 base pairs	MO, DOTAP, poloxamer 407	Quartz crystal microbalance, SAXS study of siRNA & cubosomes interactions
siRNA/22 base pairs	MO, DOTAP or DDAB, Poloxamer 407	Hexosome formation on loading, gene silencing

Formulation of Large Molecules in Cubosomes[9,11-6]

polynucleotides in the cubosomes with increasing molecular weight order.

Small Molecules

In cancer therapeutics, for example, monoolein cubosomes entrapped with doxorubicin showed an increased rate of release at lower pH. Other examples include release of folic acid in cubosomes composed of monoolein stabilized with poloxamer 407 for targeting cancer cells. Another study involves the subcutaneous administration of 5-fluouracil (5-FU) in monoolein cubosomes.[17]

Table 2 shows encapsulation of small molecule oncology drugs in cubosomes composed of monoolein and Poloxamer 407 used as a stabilizer.

Table 3 shows the cubosomes in ocular delivery of drugs composed of monoolein (GMO) and Poloxamer 407 as stabilizer.

Whilst the list of drugs encapsulated in cubosomes is exhaustive, environmental factors, such as pH, temperature, and pressure, could play an important role in drug release. Other factors include the hydrophobic and hydrophilic nature of molecules and size of interstitial hydrophobic cargo space. For example, release of lipophilic drugs, such as griseofulvin, diazepam, and propofol among others, from monoolein cubosomes is dependent upon the partition coefficient and burst mechanism that results in an immediate release within 20 mins. This can be fine turned by incorporating with pH-sensitive lipids and stabilizers to yield the sustained-release profile.[23] Cubosomes derived from phytantriol suspension encapsulated with a poorly soluble drug cinnarizine can lead to controlled-release profile over 50 hours as opposed to 5 hours from monoolein suspensions.[24] Ionic polymers incorporated in cubosomes will have direct impact on release profile of the drugs in a controlled manner. For instance, poloxamer 407 stabilized cubosomes derived from monoolein with a grafted copolymer showed an extended release at neutral and acidic pH.[25] Cubosomes derived from monoolein and Poloxamer 407 and stabilized with polyvinyl alcohol can lead to controlled release of an anti-inflammatory drug etodolac at lower dosages compared to orally administered tablets.[26] In other examples, tetrandrine-encapsulated cubosomes composed of monoolein stabilized with poloxamer 407 showed enhanced transcorneal permeation opposed to free drug.[27]

TABLE 2

Drug	Pharmacological uses	Observation
Decarbazine	First line chemotherapy for melanoma	Reduces serious side effects of IV injection, improves shelf- life, efficacy and safety
5 Fluorouracil (5-FU)	Antineoplastic agent for treatment of gastrointestinal cancers	Cubosomes increased 5-fold uptake by cancer cells as compared with dug in solution
20 (S)-Protopanaxadiol	Anticancer drug	Improved solubility & oral bioavailability

Encapsulation of small molecule oncology drugs in cubosomes composed of monoolein and Poloxamer 407 used as a stabilizer.[17-19]

TABLE 3

Drug	Pharmacological Uses	Observation
Dexamethasome (DEX)	Treatment of ocular inflammation	Increases retention time and bioavailability
Timolol (TM)	Beta blocker for treatment of glaucoma	Increased corneal penetration, prolonged corneal retention
Cyclosporine A	Immuno-supressive agent for treatment of inflammatory ocular diseases	Improved bioavailability, prolonged corneal retention

Cubosomes in Ocular Drug Delivery[20-22]

CAPABILITIES IN LIPID NANOPARTICLES

As we continue to explore new molecules with enabling innovative technologies like LipidSol, we find limitless opportunities to find the solutions for those chemical entities, making the insoluble soluble. Ascendia remains at the forefront of developing formulations of those practically insoluble and/or less bioavailable molecules and can help bring them to the advanced stages of clinics. With our expertise in formulation development built with state-of-the art GMP manufacturing capabilities, we can help innovators interested to move forward with Phase 1 and Phase 2 clinical studies. We can find the solutions quickly by employing our enabling platform technologies for formulating small and large molecules, proteins, and biologics in LNPs and cubosomes.

CONCLUSION

As we continue to explore the nanotechnologies in delivery of drugs by "making the insoluble soluble," we find cubosomes to be the most attractive lipid nanoparticles (LNPs) of all entities as they are derived from biodegradable, simple low-melting chain lipids and can be easily scaled up with high drug loading and stabilized with PEG-ylated polymers for longer shelf-life, and for efficient and sustained delivery of potent small and large molecules. Our expertise in top down and bottom formulation approaches, as outlined in Figure 2, can lead to smarter design and delivery of innovative molecules across all modalities. As we embark on expanding our state-of-the art

cGMP manufacturing facilities for sterile drug products, we expect more new molecules will be evaluated in LNPs, especially at least some preferably utilizing cubosomes in the future. ◆

REFERENCES

1. H. Umar, H. A. Wahab, A. M. Gazzali, H. Tahir and W. Ahamd, Cubosomes: Design, development and tumor targeted drug delivery applications, Polymer, 2022, 14, 3118.
2. H. M. G. Barriga, M. N. Holme, and M. M. Stevens, Cubosomes; the next generation of smart lipid nanoparticles?, Angew. Chem. Int. Ed. Eng., 2019, 58, 2958-2978.
3. B. Angelov, A. Angelova, M. Drechsle, V. M. Garamus, R. Mutafchieva, and S. Lesieur, Identification of large channels in cationic PEGylated cubosome nanoparticles by synchrotron radiation SAXS and Cryo-TEM imaging, Soft Matter. 2015; 11:3686–3692.
4. J, Huang and S. Ali, LIPIDSOL®: The Liposomes - Chemistry, Properties and Applications of Lipid Nanoparticles, Drug Dev. Delivery, 2023.
5. V. Meli, C. Caltagirone, A. M. Falchi, S. T. Hyde, V. Lippolis, M. Monduzzi, M. Obiols-Rabasa, A. Rosa, J. Schmidt, Y. Talmon Y, and S. Murgia, Docetaxel-loaded fluorescent liquid-crystalline nanoparticles for cancer theranostics, Langmuir. 2015; 31:9566–9575.
6. R. Tenchov, R. Bird, A. E. Curtze and Q. Zhou, Lipid Nanoparticles – from liposomes to mRNA vaccine delivery, a landscape of research diversity and advancement, ACS Nano, 2021, 15, 16982-17015.
7. Nakano M, Sugita A, Matsuoka H, et al. Small angle x–ray scattering and 13C NMR investigation on the internal structure of cubosomes, Langmuir. 2001, 17, 3917–3922.
8. P. T. Spicer, Progress in liquid crystalline dispersions: Cubosomes, Curr. Opinion Colloid Interface Sci. 2005, 10, 274-279.
9. (a) S. B. Rizwan, D. Assmus, A. Boehnke, T. Hanley, B. J. Boyd, T. Rades, S. Hook, Preparation of phytantriol cubosomes by solvent precursor dilution for the delivery of protein vaccines, Eur. J Pharm. Biopharm. 2011, 79, 15-22; (b) S. B. Rizwan, W. T. McBurney, K. Young, T. Hanley, B. J. Boyd, T. Rades and S. Hook, Cubosomes containing the adjuvants imiquimod and monophosphoryl lipid A stimulate robust cellular and humoral immune responses, J. Cont. Release, 2013, 165, 16-21.
10. S. P. Akhlaghi, I. R. Ribeiro, B. J. Boyd and W. Loh, Impact of preparation method and variables on the internal structure, morphology, and presence of liposomes in phytantriol-Pluronic(®) F127 cubosomes, Colloids Surfaces B Biointerfaces. 2016, 145, 845-853.
11. S. J. Fraser, X. Mulet, L. Martin, S. Praporski, A. Mechler, P. G. Hartley, A. Polyzos, and F. Separovic, Surface immobilization of bio-functionalized cubosomes: Sensing of proteins by quartz crystal microbalance, Langmuir, 2012, 28, 620-627.
12. X. Che, Z. Wang, Y. Liu , Y. Sun, and H. Liu, Sustained release of nerve growth factor from highly homogenous cubosomes stabilized by β-casein with enhanced bioactivity and bioavailability, RSC Adv. 2016, 6, 114676-114684.
13. J. Zhai, L. J. Waddington, T. J. Wooster, M-I. Aguilar, and B. J. Boyd, Revisiting β-casein as a stabilizer for lipid liquid crystalline nanostructured particles, Langmuir. 2011; 27:14757-14766.
14. C. Leal, N. F. Bouxsein, K. K. Ewert, and C. R. Safinya. Highly efficient gene silencing activity of siRNA embedded in a nanostructured gyroid cubic lipid matrix, J. Am. Chem. Soc. 2010, 132, 16841-47.
15. B. Tajik-Ahmadabad, A. Mechler, B. W. Muir, K. McLean, T. M. Hinton, F. Separovic and A. Polyzos, Chem. Bio. Chem. 2017; 18:921-930.
16. G. Zhen, T. M. Hinton, B. W. Muir, S. Shi, M. Tizard, K. M. McLean, P. G. Hartley, and P. Gunatillake, Glycerol monooleate-based nanocarriers for siRNA delivery in vitro, Mol. Pharm. 2012; 9:2450-2457.
17. X. Jin, Z. H. Zhang, S. L. Li, E. Sun, X. B. Tan, J. Song, and X. B. Jia, A nanostructured liquid crystalline formulation of 20 (S)-protopanaxadiol with improved oral absorption. A nanostructured liquid crystalline formulation of 20(S) protopanaxadiol with improved oral absorption, Fitoterapia, 2013. 84: p. 64-71.
18. D. Bei, T. Zhang, J. B. Murowchick and B. C. Youan, Formulation of dacarbazine-loaded cubosomes. Part III. Physicochemical characterization. AAPS PharmSciTech, 2010, 11, 1243-1249.
19. M. R. Cheng, Q. Li, T. Wan, B. He, J. Han, H. X. Chen, F. X. Yang, W. Wang, H. Z. Xu, T. Ye, and B. B. Zha, Galactosylated chitosan/5-fluorouracil nanoparticles inhibit mouse hepatic cancer growth and its side effects. World journal of gastroenterology: WJG, 2012. 18(42): p. 6076.
20. L. Gan, S. Han, J. Shen, J. Zhu, C. Zhu, X. Zhang, and Y. Gan, Self-assembled liquid crystalline nanoparticles as a novel ophthalmic delivery system for dexamethasone: improving preocular retention and ocular bioavailability. Int. J. Pharm. 2010, 396,179-187.
21. J. Huang, T. Peng, Y. Li, Z. Zhan, Y. Zeng, Y. Huang, X. Pan, C. Y. Wu, and C. Wu, Ocular cubosome drug delivery system for timolol maleate: preparation, characterization, cytotoxicity, ex vivo, and in vivo evaluation, AAPS PharmSciTech, 2017, 18, 2919-2926.
22. Y. Chen, Y. Lu, Y. Zhong, Q. Wang, W. Wu, and S Gao, Ocular delivery of cyclosporine A based on glyceryl monooleate/poloxamer 407 liquid crystalline nanoparticles: preparation, characterization, in vitro corneal penetration and ocular irritation. J. Drug Target., 2012, 20, 856-863.
23. B. J. Boyd, Characterization of drug release from cubosomes using the pressure ultrafiltration method, Int. J. Pharm. 2003, 260, 239-247.
24. T. H. Nguyen, C. J. H. Porter, I. Larson, and B. J. Boyd, Phytantriol and glyceryl monooleate cubic liquid crystalline phases as sustained-release oral drug delivery systems for poorly water soluble drugs I. Phase behaviour in physiologically-relevant media, J. Pharm. Pharmacol. 2010, 62, 856-865.
25. M. Kluzek, A. Tyler, S. Wang, R. Chen, C. M. Marques, F. Thalmann, J. M. Seddon, and M. Schmutz, Influence of a pH-sensitive polymer on the structure of monoolein cubosomes, Soft Matter. 2017, 13, 7571-7577.
26. S. Salah, A. A. Mahmoud, and A. O. Kamel, Etodolac transdermal cubosomes for the treatment of rheumatoid arthritis: ex vivo permeation and in vivo pharmacokinetic studies, Drug Deliv. 2017, 24, 846-856.
27. R. Liu, S. Wang, S. Fang, J. Wang, J. Chen, X. Huang, X. He X, and C. Liu, Liquid crystalline nanoparticles as an ophthalmic delivery system for tetrandrine: Development, characterization, and in vitro and in vivo evaluation, Nanoscale Res Lett. 2016, 11, 254.

PLATFORM TECHNOLOGY

The PTX△LNP® Platform: On the Promise of Developing New LNPs for Tomorrow's mRNA Therapies

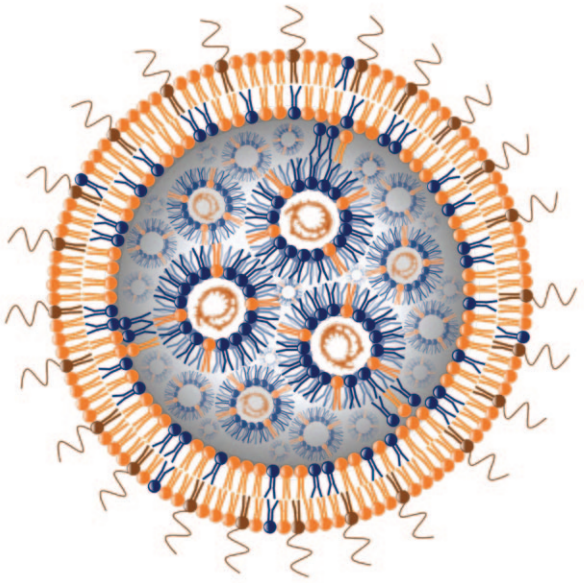
By: Charlotte Dunne, PhD, Katrin Radloff, PhD & Leonidas Gkionis, PhD

INTRODUCTION

The implementation of nanomedicine to the medical field has led to significant breakthroughs in the targeted and effective delivery of small molecules and oligonucleotide therapeutics to affected diseased areas.[1] The COVID-19 pandemic has given rise to a new era of promising modalities in the biopharmaceutical sector, with messenger-RNA (mRNA) technologies prominently taking center stage as the next generation of therapeutics and vaccines against severe pathologies.[2]

Throughout the past few decades, non-viral engineered vectors - including lipid or polymer-based ones - have been extensively developed to effectively encapsulate and protect synthetic RNA/mRNA species during systemic administration for gene delivery purposes.[3] The rationale behind the design of such nanostructured delivery systems is to achieve advanced cellular uptake at the affected site with subsequent functional endosomal escape of the nucleic acid payload into the cell cytoplasm. Additionally, these systems should exhibit low immunogenic and toxicological profiles, prolonged circulation properties, serum stability, chemical versatility, organ specificity, and facile scale-up manufacturing among the others.[4] The first well-studied and FDA-approved delivery system was liposome-based, whereas the first siRNA-LNP approved formulation, Onpattro paved the way for the newest generation of nanovectors composed of lipids encapsulating mRNAs called lipid-based nanoparticles (LNPs).[5-7] Principally, these are referred to as 3D nano-constructs comprising three, four, or even more different lipid moieties, such as ionizable and/or cationic lipids, phospholipids, cholesterol, and polyethylene glycol (PEG)-lipids (Figure 1).[8]

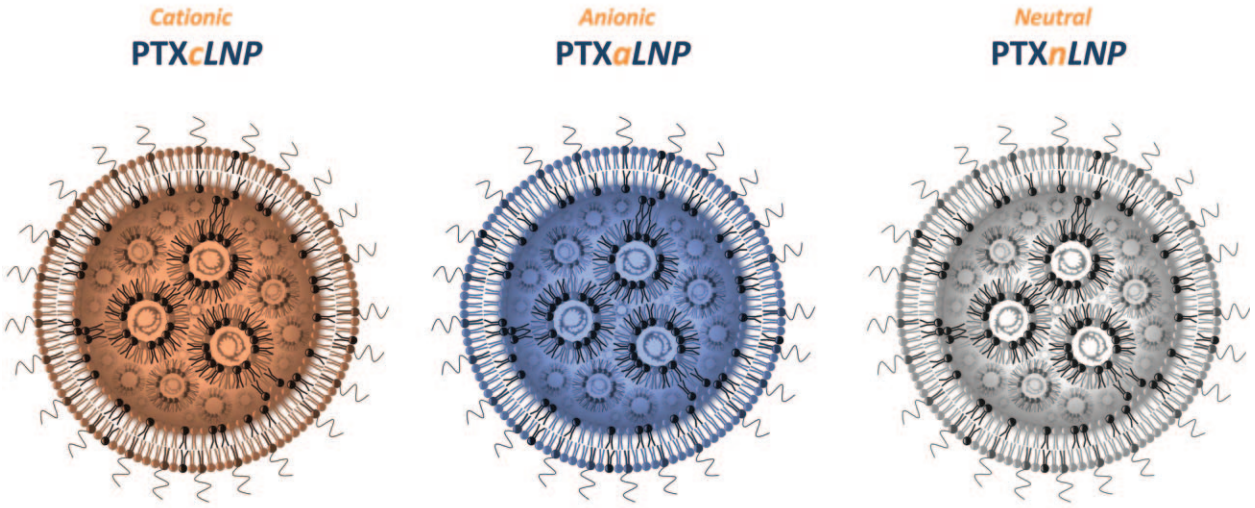
FIGURE 1



Model structure of an LNP construct entrapping mRNA. The nucleic acids intermingle with the ionizable/cationic lipid species (blue) that are widely distributed but principally occupying the central core of the particle (formation of hexagonal HII regions). Helper lipids (orange) contribute mainly to bilayer forming, whereas PEGylated lipids (brown) confer shielding properties on the surface and further stabilization to the system.

Pantherna Therapeutics engages in the development of two distinct scientific pillars, including both mRNA and LNP technology platforms as a basis for novel top-notch mRNA therapeutics against a wide spectrum of possible target diseases. The company´s PTXmRNA® technology has demonstrated superior results in terms of the expression of the desired target protein compared to commercially available mRNA. Best performance of PTXmRNA® was achieved through modifications in the codon se-

FIGURE 2



PTXcLNP (orange) has an overall cationic surface charge, PTXaLNP (blue) has an anionic surface charge, and PTXnLNP (grey) has a neutral overall surface charge.

quence, incorporating state-of-the-art capping structures, and by employing specific untranslated sequence regions flanking the coding region. These modifications have demonstrated superior expression most likely through optimized ribosome loading and scanning for multiple mRNA protein targets. Additionally, the PTXΔLNP® platform offers a synergistic sister technology to the mRNA platform to obtain potent mRNA-LNPs for therapeutic applications.

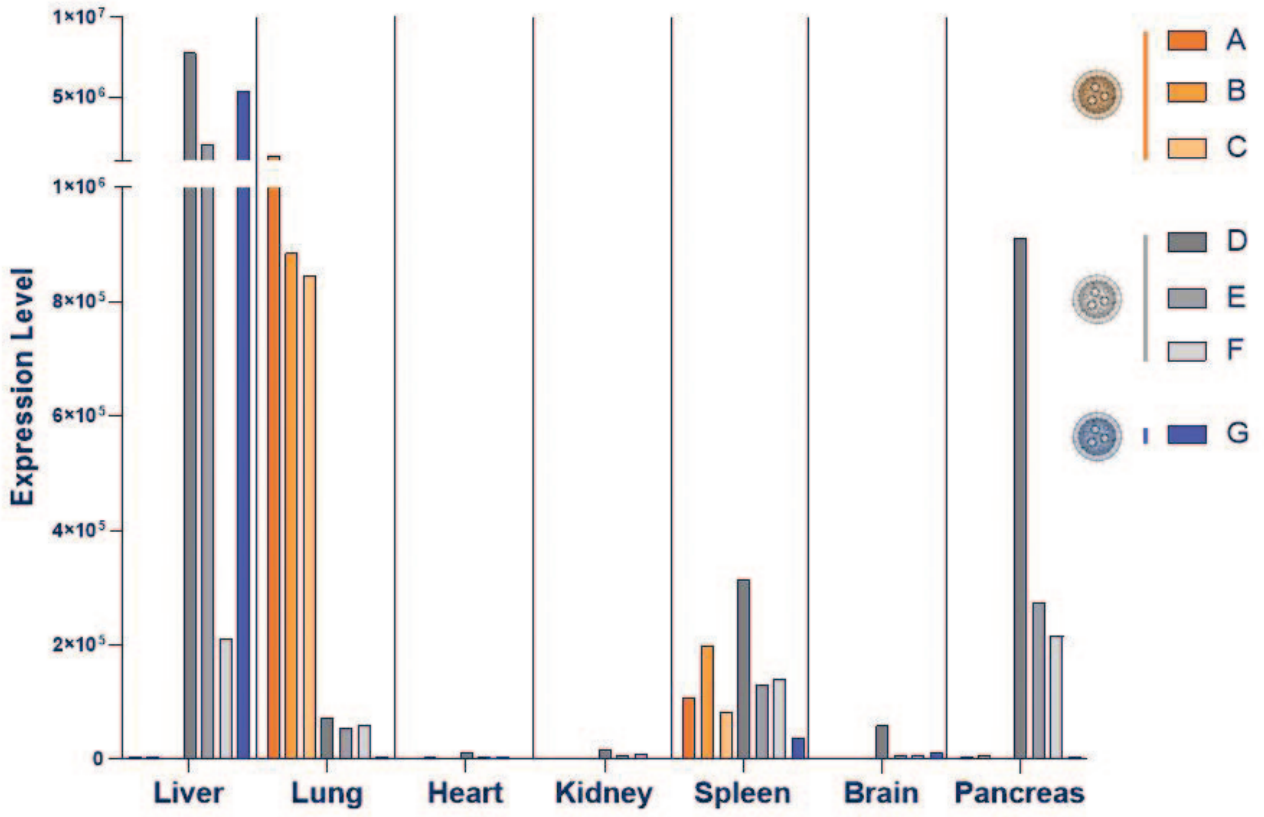
The LNP formulation and manufacturing process is of essential importance for the precise control and prediction of the particle's intrinsic characteristics, especially when aiming for clinical translation. Conventional preparative methods, such as solvent-injection, and automated microfluidic systems are widely implemented for cost-effective and facile scaled-up production of LNPs nowadays. Progress in the development of flow chemistry mixing has proven to adequately meet the requirements for ease and feasibility over the industrial scalability of LNPs. Various peers, such as BioNTech/Acuitas and Moderna, invested into the research development of mRNA LNP formulas for over a decade, which during the COVID-19 pandemic, resulted in the well-known formulated COVID-19 vaccine suspension. The underlying mRNA-LNP as in the case of BNT162b2 (Comirnaty®) consists of four structural lipids, namely the ionizable lipid ALC-0315, the two helpers Cholesterol and Distearoylphosphatidylcholine (DSPC), and the PEGylated lipid ALC-0159, and the formula is approved for intramuscular injection.[9]

Pantherna's proprietary formulations entail chemically versatile lipidic systems that bear ultimately three different physicochemical attributes, namely their overall surface charge: neutral (nLNPs), cationic (cLNPs), and anionic (aLNPs) (Figure 2). nLNPs and aLNPs are basically categorized in the standardized four-lipid compositional scheme, whereas the cLNP corresponding derivatives comprise mainly of three lipid moieties, which practically favors more cost-effective manufacturing. Through continuous fine-tuning over the established manufacturing processes, the overall objective of Pantherna is to ensure high levels of scalability, reproducibility, and cost-effectiveness for their LNP pipeline platform. The design simplicity of their LNP systems ensures robust physicochemical stability of the lipid suspensions produced (monodisperse sizes, versatile surface charges, batch-to-batch consistency, high oligonucleotide encapsulation rates), and primarily a safe toxicological profile paving the way toward promising clinical translation.

Pantherna's delivery platform assets are organ selectivity and cell type specificity of the LNPs. Figure 3 illustrates the *in vivo* biodistribution profile of selected LNP formulations derived from the platform, upon intravenous administration in mice models. Pantherna's formulations can confer more direct organ-specificity with their cLNPs (orange bars) demonstrating high expression in lung tissue and with one aLNP formula (blue bars) showing selective expression in the liver tissue but without any prominent activity in the remaining organs. The nLNPs (grey bars) demonstrate prominent liver-directed expression rates, with one nLNP candidate formulation also effectively targeting the pancreatic tissue.

The dynamic of Pantherna's technology platforms is exemplified by PAN004, which is the lead candidate formulation for systemic administration. PAN004 is a

FIGURE 3



***In vivo* biodistribution data of cationic (orange), anionic (blue), and neutral (grey) PTXΔLNPs revealed by mRNA reporter expression in different tissue extracts.**

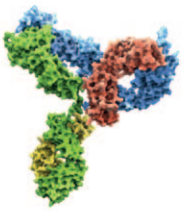
novel synthetic, nucleoside-modified mRNA encoding COMP-Ang1 (mRNA-76b) formulated with PTX cationic lipid nanoparticle (PTXcLNP002) making use of a proprietary cationic lipid within a three-lipid moiety formulation. The highly selective delivery to the lung was demonstrated in suitable *in vivo* experiments, sparing other vascular beds, and bypassing the liver. Single cell RNA-sequencing confirmed lung endothelial delivery specificity of the therapeutically active component COMP-Ang1 PTXmRNA® after PAN004 was administered intravenously. PAN004 is intended to enable high spatial expression and thereby positioning of a hyperactive Tie2- agonist to counteract the progression of acute respiratory distress syndrome (ARDS), which is composed of leaky lung endothelium and is caused by various events, such as sepsis, pneumonia, or COVID-19. In the acute phase of ARDS, pulmonary edema is a hallmark pathophysiological event that is accompanied by neutrophil influx and inflammatory cytokine production that leads later to fibrosis, epithelial damage, and life-threatening respiratory dysfunction. There is an unmet medical need as lethality of ARDS is still high at 30%-40%.[10] PAN004 acts in the acute phase by stabilizing the endothelial barrier and therefore counteracts edema and neutrophil influx exemplifying the therapeutic potential of mRNA-therapies beyond vaccination.[11]

In addition to Pantherna's lead development program, further innovative mRNA and LNP combinations from the platform exhibited promising prospects across a range of pathologies. Alongside lung, liver, and pancreas, the PTX portfolio possesses LNP formulations also suitable for local delivery, such as intramuscular administration or even for *ex vivo* application. In addition to applications for myocyte-directed target gene expression, eg, in regenerative medicine, the PTXΔLNP® platform orients particularly toward cancer vaccination for efficient immunization. The functionality of PTXΔLNPs for immunization was recently disclosed through a collaboration with Evaxion Biotech.[12] The combination of PTXΔLNPs and Evaxion's AI-identified cancer vaccine antigens encoded by a PTXmRNA® induced a robust T cell response against the tumor antigens *in vivo* while simultaneously eliminating the tumor growth of the syngeneic tumors in mice. The results of this study establish the potential of PTXΔLNPs as very efficient mRNA-LNP cancer vaccine tools.

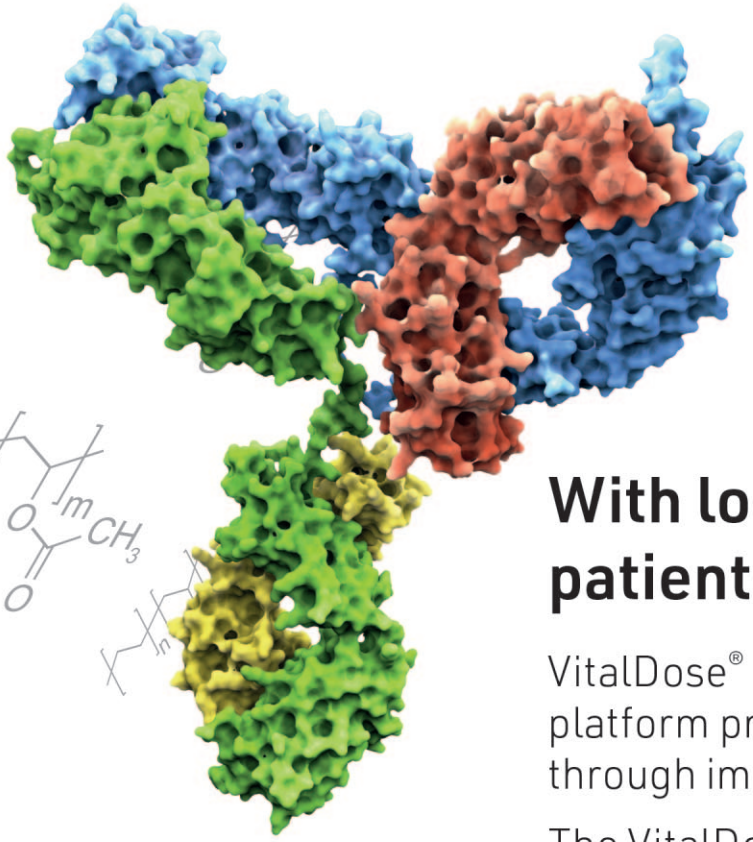
Immune cell targeting is important in cancer vaccines, infectious diseases, and

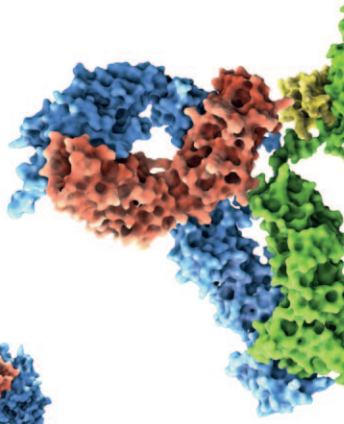
Celanese

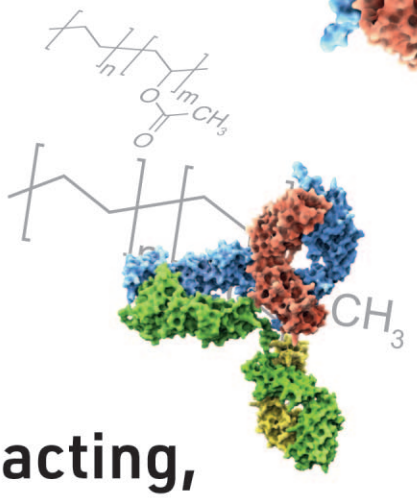
VITAL Dose®



Sustained Drug Delivery







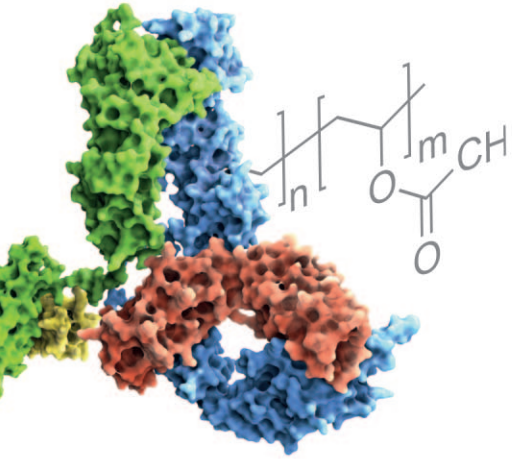
With long-acting, patient-centric therapeutics

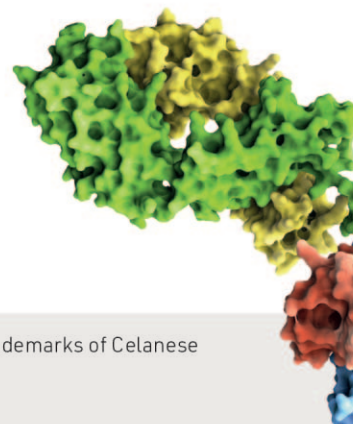
VitalDose® EVA is a copolymer drug-delivery platform providing controlled release through implant and insert dosage forms.

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

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

- mAbs
- RNA
- Small molecules





Collaborate with us

Email: Healthcare@Celanese.com

Website: Healthcare.Celanese.com

in autoimmune disorders. Pantherna holds promising data that demonstrate selective immune cell uptake of our developed LNPs with positive uptake in monocytes and macrophages. Specific targeting of these immune cells can be envisioned for many different purposes and provides prospects for their use in immunization against infectious diseases and in autoimmune disorders, such as systemic sclerosis, rheumatoid arthritis, primary biliary cholangitis, Sjogren's syndrome, and inflammatory bowel disease.[13,14] Currently, immune cell utilization in therapies involves time and expensive processes with the isolation of T cells or monocytes directly from each individual patient, genetic editing/ re-programming or re-activation of the cells, and re-introduction back to the patient.[15] This method comes with challenges, including difficulties in viral transduction and transfection of cells and keeping them free from contamination by treating them only in a closed-circuit environment. Efforts are being made in the development of allogeneic "off-the-shelf" cell therapies, using cryopreserved cells modified from donors, although, these therapies would reduce costs and offer faster treatments to patients; however, the risk of graft-rejection from allogenic cells may be life-threatening.[16] The use of Pantherna's LNP-platforms for non-viral *ex vivo* application could increase the number of transfected cells and the subsequent production of the target mRNA, enhancing the efficiency and reducing toxicity during the production of autologous and allogenic cell therapies. Circumvention of *ex vivo* transfection with systemic administration of adenosine-associated virus (AAV) has demonstrated *in vivo* generated CAR-T cells leading to positive *in vivo* tumor regression.[17] However, the known downside of viral therapies is that the effects are permanent, whereas LNPs can offer an alternative transient therapeutic approach. In the long run, optimized PTXΔLNPs prospectively bypass *ex vivo* cellular handling altogether by intravenous injection to specifically target and transfect the desired immune cell population, potentially circumventing the costly and risky processes of adoptive immune cell therapies.

In summary, the PTXmRNA® and PTXΔLNP® platforms offer a readily usable technology platform for selective delivery to different organs and immune cells for any given administration route providing the basis for promising future novel mRNA therapies. ◆

REFERENCES

1. L. Brannon-Peppas and J. O. Blanchette, 'Nanoparticle and targeted systems for cancer therapy', Advanced Drug Delivery Reviews, vol. 56, no. 11. Elsevier, pp. 1649-1659, Sep. 22, 2004.doi:10.1016/j.addr.2004.02.014.
2. E. Rohner, R. Yang, K. S. Foo, A. Goedel, and K. R. Chien, 'Unlocking the promise of mRNA therapeutics', Nature Biotechnology, vol. 40, no. 11. Nature Research, pp. 1586–1600, Nov. 01, 2022. doi: 10.1038/s41587-022-01491-z.
3. H. Zu and D. Gao, 'Non-viral Vectors in Gene Therapy: Recent Development, Challenges, and Prospects', AAPS Journal, vol. 23, no. 78. Springer Science and Business Media Deutschland GmbH, pp. 1-12, Jul. 01, 2021. doi: 10.1208/s12248-021-00608-7.
4. S. Qin et al., 'mRNA-based therapeutics: powerful and versatile tools to combat diseases', Signal Transduction and Targeted Therapy, vol. 7, no. 1. Springer Nature, Dec. 01, 2022. doi: 10.1038/s41392-022-01007-w.
5. H. Daraee, A. Etemadi, M. Kouhi, S. Alimirzalu, and A. Akbarzadeh, 'Application of liposomes in medicine and drug delivery', Artificial Cells, Nanomedicine and Biotechnology, vol. 44, no. 1. Taylor and Francis Ltd., pp. 381-391, Jan. 01, 2016. doi: 10.3109/21691401.2014.953633.
6. H. Xing, K. Hwang, and Y. Lu, 'Recent developments of liposomes as nanocarriers for theranostic applications', Theranostics, vol. 6, no. 9. Ivyspring International Publisher, pp. 1336-1352, 2016. doi: 10.7150/thno.15464.
7. Akinc, A., Maier, M. A., Manoharan, M., Fitzgerald, K., Jayaraman, M., Barros, S., Cullis, P. R. (2019). The Onpattro story and the clinical translation of nanomedicines containing nucleic acid-based drugs. Nature Nanotechnology, 14(12), 1084-1087. doi:10.1038/s41565-019-0591-y.
8. M. Mendonça, A. Kont, P S. Kowalski, and C. O'Driscoll, 'Design of lipid-based nanoparticles fordelivery of therapeutic nucleic acids', Drug Discov Today, vol. 28, no. 3, pp. 1-17, 2023.
9. L. M Lewis, A. V Badkar et al., 'The Race to Develop the Pfizer-BioNTech COVID-19 Vaccine: From the Pharmaceutical Scientists' Perspective', Journal of Pharmaceutical Sciences 112 (2023) 640−647.
10. M. A. Matthay et al., 'Acute respiratory distress syndrome', Nat Rev Dis Primers, vol. 5, no. 1, 2018, doi: 10.1038/s41572-019-0069-0.
11. K. Radloff, B. Gutbier, C. Dunne, et al., 'Spatial expression of an mRNA encoding Tie2-agonist in the capillary

endothelium of the lung prevents pulmonary vascular leakage', bioRxiv 2022.10.12.511878, 2022, doi: 10.1101/2022.10.12.511878.

12. Evaxion and Pantherna announce promising preclinical mRNA vaccine data. EVAXION. Retrieved May 12, 2023, from https://www.evaxion-biotech.com/press-releases/080223-evaxion-and-pantherna-announce-promising-preclinical-mrna-vaccine-data.
13. W. T. Ma, F. Gao, K. Gu, and D. K. Chen, 'The role of monocytes and macrophages in autoimmune diseases: A comprehensive review', Frontiers in Immunology, vol. 10, no. 1140. Frontiers Media S.A., pp. 1-24, 2019. doi: 10.3389/fimmu.2019.01140.
14. Chaudhary, N., Weissman, D. & Whitehead, K.A. mRNA vaccines for infectious diseases: principles, delivery and clinical translation. Nat Rev Drug Discov 20, 817–838 (2021). https://doi.org/10.1038/s41573-021-00283-5.
15. Köhl, U., Arsenieva, S., Holzinger, A. & Abken, H. 'CAR T cells in trials: recent achievements and challenges that remain in the production of modified T cells for clinical applications', Hum. Gene Ther, 29, 559-568 (2018).
16. Depil S, Duchateau P, Grupp SA, Mufti G, Poirot L. "Off-the-shelf" allogeneic CAR T cells: development and challenges', Nat Rev Drug Discov, 2020 Mar;19(3):185-199. doi: 10.1038/s41573-019-0051-2. Epub 2020 Jan 3. PMID: 31900462.
17. Nawaz, W., Huang, B., Xu, S. et al. AAV-mediated in vivo CAR gene therapy for targeting human T-cell leukemia. Blood Cancer J. 11, 119 (2021). https://doi.org/10.1038/s41408-021-00508-1.

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

BIOGRAPHIES

Dr. Charlotte Dunne a scientist in the R&D department at Pantherna Therapeutics. She recently joined the company in 2023. Prior to that, she worked as a Postdoc at Helmholtz-Zentrum Hereon and Berlin Center for Regenerative Therapies at Charité, Germany. She earned her PhD in Pharmacology from the University of Auckland at the Centre for brain research, New Zealand in 2022. She has experience in working with vascular cells and degenerative diseases.

Dr. Katrin Radloff is a scientist in the R&D Department at Pantherna Therapeutics. She joined the company in 2020 working on the development of PAN004. Prior to that, she has worked as a Postdoc on NMR-based metabolomics in the Department of Physiology and Biochemistry of Nutrition and the Max-Rubner-Institut in Karlsruhe, Germany. During her PhD, she investigated inflammation resolution pathways in gastrointestinal cancer at the institute of biomedical science at the University of São Paulo, Brazil.

Dr. Leonidas Gkionis is a scientist in the R&D Department at Pantherna Therapeutics. He joined the company in 2022 working on the design and production of cutting-edge formulations. Prior to that, he worked as a Galenical Formulation Scientist at different pharmaceutical industries. He earned his PhD in Nanomedicine from the University of Manchester, UK, as part of the Graphene NOWNano CDT sponsored by EPSRC. He holds hands-on professional experience in the pharmaceutical manufacturing of small drug molecules and recently of oligonucleotides.

Why PharmaCircle?

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

PHARMACIRCLE™

www.pharmacircle.com

Pipeline & Products Intelligence

Business Intelligence & Prospecting Tools

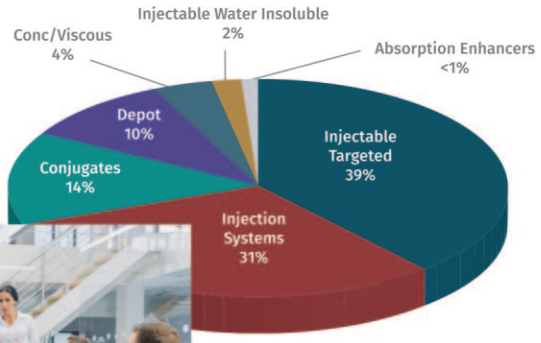
Research & Development Analysis Tools

Regulatory Databases & Documents

View Formulation and Component Details

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

Evaluate New and Promising Technologies



Injectable Drug Delivery Technologies

Screen Potential Partnering and Investment Opportunities

Assess Development Pipelines and The Competitive Landscape

PHARMACIRCLE™

Schedule Your Demo

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

www.pharmacircle.com

SOLUBILIZING & STABILIZING TECHNOLOGY

CAPTISOL® - Part Perseverance & Part Serendipity

By: Vince Antle, PhD, James Pipkin, PhD, and Lian Rajewski, PhD

INTRODUCTION

While Captisol (Betadex Sulfobutylether Sodium) is a remarkable narrative of a successfully functional excipient broadly accepted as the premier solubilizing and stabilizing technology by the pharmaceutical industry, with 15 approved Captisol-enabled drug products, it was far from a certainty early on. Many steps along the way could have prevented Captisol from becoming a reality. It has taken the perseverance of many of our scientists, early believers, and exceptional partners to bring this important excipient to the pharmaceutical industry.

FROM THESIS TO DISCOVERY

Dr. Roger Rajewski recounts his thesis work on the modified cyclodextrin Captisol: "Back in the late 80s over a beer with Dr. Valentino Stella, we discussed one last attempt to prepare a safe, pharmacologically inactive, but highly soluble, sulfobutylether beta cyclodextrin that could retain its broad utility to form host-guest complexes with a wide array of molecules. If this last-ditch effort, after almost 5 years of failed attempts, wasn't successful, the modified cyclodextrin work would cease, and I would finish my graduate degree on an oral prodrug project." [1] The last-ditch effort worked.

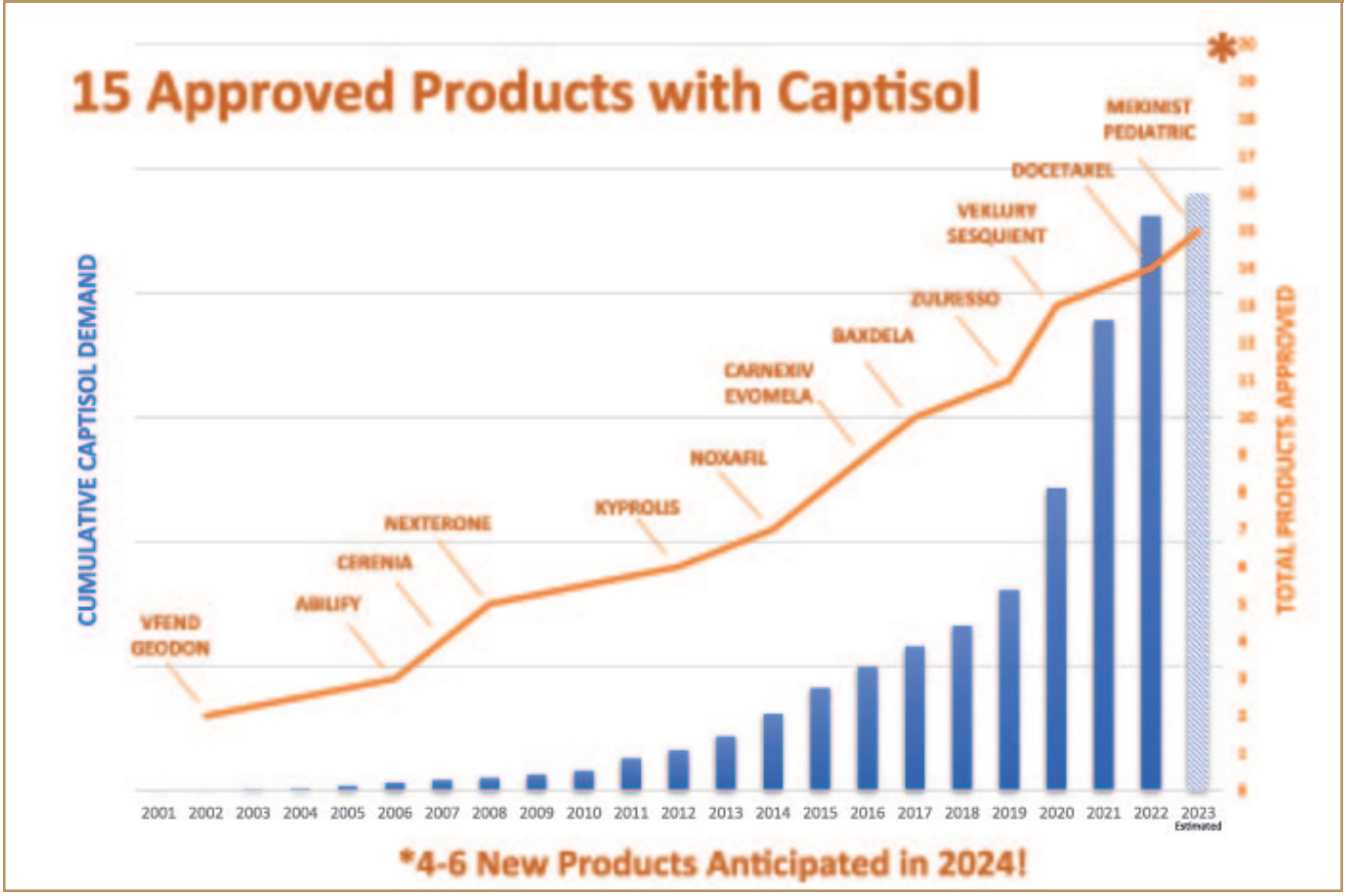
The motivation to create this tool for formulators of poorly soluble and unstable molecules, which were growing with the advent of high throughput screening, was especially strong in the Pharmaceutical Chemistry Department at Kansas University. Being one of several academic labs that had contracts with the National Cancer Institute, it oversaw the study of many challenging new chemical entities and created initial formulations that allowed these compounds a development path forward.

PFIZER PLAYED A CRUCIAL ROLE

If Captisol had not found an early adopter and willing partner like Pfizer in the development of the technology, it is certain the technology would have come to an end. It was serendipity that brought Pfizer to examine Captisol as an alternative solubilizing agent. After several encouraging animal studies and early formulation development work, Pfizer was unable to continue

In 2023, Aldeyra Therapeutics, Inc. announced the US FDA accepted the NDA for topical ocular reproxalap.

FIGURE 1



using the proprietary hydroxypropyl beta-cyclodextrin and pivoted to a relatively unknown new modified beta-cyclodextrin known as sulfobutylether beta-cyclodextrin (SBECD aka Captisol) based on subtle safety benefits observed in animal models.[2,3] If not for the work of many at Pfizer, process chemistry and safety studies for Captisol would not have been completed. A pivotal licensing agreement led to the generation of the IND-enabling characterization, pharmacology, and safety data on Captisol; this data generated by Pfizer was the basis for the Captisol safety Drug Master File, and later added to by the Captisol Team and other partners.[4]

The needs of our partners motivated us to create Drug Master Files in other countries to help support their drug products. Over the past decades, new Master Files have been established in Canada, China, and Japan. To date, there are five Captisol Drug Master Files around the world, CMC (Type IV) and safety (Type V) in the US, and CMC in Canada, China, and Japan. These files have also supported our partners in their clinical and commercial development of their drug products using oral, ophthalmic, nasal, inhalation, and parenteral routes of delivery.

SAFETY IS KEY

The proven safety of Captisol technology is one of its distinguishing features. From inception to its use in patients, safety is a key element to the successful introduction and persistence of Captisol as a mainstay formulation tool. Beginning with the chemical structure, the sulfobutyl ether group was identified as among the best moieties and spacer for improving the solubility of the parent cyclodextrin and being one of the safest modified beta-cyclodextrins by mitigating the nephrotoxic effect of the parent beta-cyclodextrin.

Throughout the past 20 years, much has been done to improve the purity of Captisol, including lowering the content of sultone, chloride, and endotoxins in the all-aqueous manufacturing process. The Captisol Team has a commitment to quality and safety. Our team has worked side by side with partners to better understand their products and the best way to use Captisol in their formulations. Through these collaborations, previously unknown impurities were discovered that were affecting the stability of actives. Ultimately, through a Continuous Improvement Program with Hovione, the contract manufac-

SQ Innovation Submitted NDA for Furosemide with Captisol in a subcutaneous infusion patch pump.

turer of Captisol, phosphate was removed, and other impurities were significantly reduced with extensive carbon processing steps. Much care is taken during the manufacturing, processing, and packaging to minimize impurities and ensure quality and reproducibility.

FIRST PRODUCT

Along with the new millennium, the first drug product approved in the US using Captisol brought recognition to the technology as the first safe, anionic modified cyclodextrin that could be administered intravenously. In 2002, VFEND IV (Pfizer) was the first Captisol-enabled product approved by the FDA. In fact, the first three approved Captisol-containing products were Pfizer products. Today, Captisol is in 15 FDA-approved products, many of which are globally accepted in more than 160 countries.

PRODUCTION READY

The process of isolating Captisol commercially has evolved. At the outset, concentrated aqueous Captisol solutions were tray freeze-dried in small batches, then spray dried into fine powder at 150-kg scale; a more free-flowing granular solid was then produced by spray agglomeration at 2,500 kg per batch. Each of these form/scale changes achieved the goal of manufacturing scale-up with the same or better quality to give clients the ability to work with different physical forms.

In 2019, our partner Gilead requested that Captisol production be ramped up for their antiviral COVID-19 treatment. Throughout the next 12 months, the Captisol Team and our manufacturing partner Hovione successfully completed 12 process validations throughout the Captisol manufacturing process, qualifying two new key raw material suppliers, and three new spray-dry isolation sites. If not for the need of the lifesaving VEKLURY (remdesivir) product, the only FDA-approved antiviral treatment for COVID-19, there would have been no need to increase the batch size to 7,500 kg and expand Captisol annual capacity to 400,000 kg. The pandemic and resourcefulness in response to expand material production have forever improved Captisol production readiness for all future needs.

NEW ROUTES OF DELIVERY

Throughout the past 20 years, all Captisol-enabled products that were approved have been either intravenous or intramuscular injectables. Other routes of administration have been used in clinical trials and routes previously considered novel are just now being approved. The need for other routes of administration by

COME MEET US AT:

AAPS ORLANDO, FL
OCT 22-25, BOOTH 2285

CPHI BARCELONA
OCT 24-26, BOOTH 80J39

SEVER
PHARMA SOLUTIONS

WE BRING YOUR PHARMACEUTICAL IDEAS TO LIFE

Sever Pharma Solutions is your committed CDMO specializing in HPAPI in a range of dosage forms including Polymer based dosage forms like rings and implants, Aseptic Fill & Finish syringes and Hot-melt extrusion OSD.

severpharmasolutions.com

partners and their therapeutic goals have propelled the technology forward. For instance, in 2019, in collaboration with a partner, work began on a carcinogenicity study for Captisol that would enable our partner's product, and others, for chronic oral use. The study was successfully completed and is being added to the safety Drug Master File.

The previous success and continued value in Captisol-enabled formulations being developed is largely due to the hard work and diligence of product sponsors and the relationship with Captisol technology experts. The Captisol Team has been integrally involved in overcoming development hurdles. These challenges have included drug product particulate issues, impurities, stability, biowaivers, and other regulatory obstacles.

This year, the Captisol Team celebrated a new route of administration with the approval of a pediatric oral product (Novartis-MEKINIST). In late 2023/early 2024, additional Captisol-enabled products may be approved for an ophthalmic eye drop for dry eye and for a wearable subcutaneous pump product. The ultimate benefit of Captisol technology is that tens of millions of patients have been positively affected by drugs that may not otherwise have been available. Other routes are also being explored clinically including inhalation, nasal, and dermal.[5-7]

High Density Microarray Patch (HD-MAP)
From www.VAXXAS.com

RENAL SAFETY

Despite the 20-plus years of patient experience, partners and regulatory agencies still had concerns about the renal safety of Captisol in severely renally impaired patients. Such concerns have been raised because Captisol is eliminated by glomerular filtration and has the potential to accumulate in patients with compromised renal function, as stated in the label for the first approved Captisol-containing product VFEND IV:

"In patients with moderate or severe renal insufficiency (creatinine clearance <50mL/min), accumulation of the intravenous vehicle, SBECD, occurs. Oral voriconazole should be administered to these patients, unless an assessment of the benefit/risk to the patient justifies the use of intravenous voriconazole. Serum creatinine levels should be closely monitored in these patients, and, if increases occur, consideration should be given to changing to oral voriconazole therapy."

Because many patients needing antifungals are seriously ill and have comorbidities, such as chronic kidney disease with impaired renal function, the more information the better to inform the broadest use to treat and save lives. Hence, the use of Captisol-containing products in the renally impaired patient has been much contemplated and clinically evaluated.

To our knowledge no correlation between Captisol exposure and renal issues have been found in spite of the abundance of data, which includes decades of use and studies of Captisol in patients with impaired renal function. In fact, one recent article indicates the Captisol-enabled IV voriconazole administered to critically ill patients with impaired renal function was not associated with renal deterioration or an increase in mortality.[8]

In another approved Captisol-enabled product, BAXDELA (Melinta 2017), clinical studies were performed in renally compromised subjects. One study was designed to characterize the pharmacokinetics and tolerance of SBECD in subjects with all stages of renal impairment, including subjects with end-stage renal disease (ESRD) undergoing hemodialysis and concluded:[9]

"Increased SBECD exposures did not result in any noticeable increase in drug-related TEAEs in this study." And "… decreasing renal function causes reduced SBECD (Captisol) clearance and increased exposures, but SBECD continues to exhibit a good safety and tolerability profile in IV formulations."

A vitally important Captisol-enabled medicine used to treat severe COVID-19 was first granted an EUA in May 2020 and became the first and only approved antiviral product to treat COVID-19 in October 2020. The original label advised against use in severe renally impaired patients and required estimated glomerular filtration rate (eGFR) monitoring based on a broad generalization about accumulation and increased exposure to SBECD without any correlation to actual functional harm in humans.

Immediately, questions and concerns were raised related to use in severe renally compromised patients. Again, the literature reflected the ongoing debate until recently, when Gilead completed and reported results from a large randomized controlled multicenter trial that evaluated the safety of Veklury in patients with moderately and severely reduced kidney function who were hospitalized for COVID-19, a population with increased COVID-19-related mortality.[10] The trial included 243 hospitalized adult participants with confirmed COVID-19 and renal impairment, including subjects with acute kidney injury or chronic kidney disease with end-stage kidney disease requiring hemodialysis. The trial concluded:

"…No new safety signals were observed in the study and no additional adverse reactions to Veklury were identified in 163 hospitalized patients with AKI (n=60), CKD (n=44) or ESKD (n=59) on hemodialysis receiving Veklury for up to 5 days."

TRIALS RESULT IN NEW LABEL LANGUAGE

Importantly, this clinical safety data supported the approval of new label language in July 2023, removing the need for eGFR monitoring. Hence, VEKLURY became the first approved antiviral treatment for COVID-19 patients across all stages of renal disease. Furthermore, the renal language pertaining to SBECD in Section 8.6 and 12.3 in the label became just the observations from the trial. The new section of 8.6 now states:

"…the metabolites of remdesivir, and SBECD are increased in subjects with mild to severe renal impairment, including those requiring dialysis, relative to subjects with normal renal function…No dosage adjustment of VEKLURY is recommended for patients with any degree of renal impairment, including those on dialysis…"

The new section of 12.3 now states:

"Exposures of GS-441524, GS-704277, and SBECD were up to 7.9-fold, 2.8-fold, and 21-fold higher, respectively, in those with renal impairment compared to those with normal renal function... These changes are not considered to be clinically significant…"

New products, new clinical studies, and real-world results pave the way for better informed labeling for Captisol-containing products.

THE PROMISE OF CAPTISOL

With decades of experience, proven safety, and recent and forthcoming authorizations in several new routes of delivery, the Captisol Team is looking forward to the next 2 decades and more new drug products, new applications, and continued improvement in CAPTISOL technology.

We maintain a broad global patent portfolio for Captisol, with approximately 440 issued patents worldwide relating to the technology (including 45 in the US) and with the latest expiration date in 2035. Other patent applications covering methods of making Captisol, if issued, extend to 2041. In addition to cGMP-manufactured solid Captisol powder, we offer our partners access to aqueous Captisol concentrate. This product offering was established to reduce cycle time and increase Captisol production capacity for large-volume drug products. ◆

REFERENCES

1. Personal communication September 2023.
2. Valentino J. Stella and Roger A. Rajewski (2020) Sulfobutylether-β-cyclodextrin, International Journal of Pharmaceutics, Jun 15;583:119396. doi.org/10.1016/j.ijpharm.2020.119396
3. Luke DR, Tomaszewski K, Damle B, Schlamm HT. Review of the basic and clinical pharmacology of sulfobutylether-beta-cyclodextrin (SBECD). J Pharm Sci. 2010 Aug;99(8):3291-301. https://doi.org/10.1002/jps.22109 PMID: 20213839.
4. Furness, Guy. Partnering With Big-Pharma: Pfizer & CyDex's Positive Experience: A Case Study. Drug Delivery and Technology January 2006, Vol. 6 No. 1
5. Study in Participants With Early Stage Coronavirus Disease 2019 (COVID-19) to Evaluate the Safety, Efficacy, and Pharmacokinetics of Remdesivir Administered by Inhalation, NCT04539262. ClinicalTrials.gov, 2020.
6. L. M. Pozza, A. Salapatek, D. Patel, J. Pipkin, R. Zimmerer, Jr., P. Patel; Ocular Symptoms Are Significantly Improved by Budesonide Nasal Solution (Captisol-Enabled®) Compared to Micronized Suspension (Rhinocort Aqua®) or Placebo in Patients With Seasonal Allergic Conjunctivitis (SAC) Studied in an Environmental Exposure Chamber (EEC) Model. Invest. Ophthalmol. Vis. Sci. 2008;49(13):423.
7. Forster AH, Witham K, Depelsenaire ACI, Veitch M, Wells JW, Wheatley A, et al. (2020). Safety, tolerability, and immuno-

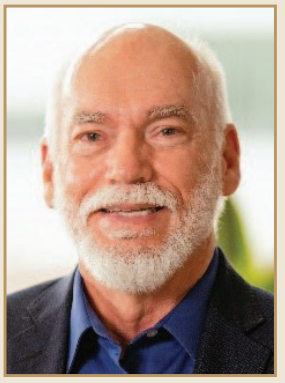
genicity of influenza vaccination with a high-density microarray patch: Results from a randomized, controlled phase I clinical trial. PLoS Med 17(3): e1003024. https://doi.org/10.1371/journal.pmed.1003024

8. Linlin Wang and Zanling Zhang (2022) Comment about the safety of intravenous voriconazole formulated with sulfobutylether beta-cyclodextrin, Expert Opinion on Drug Safety, 21:1, 133-134. https://doi.org/10.1080/14740338.2021.1978976
9. Hoover RK, Alcorn H Jr, Lawrence L, Paulson SK, Quintas M, Luke DR, Cammarata SK. Clinical Pharmacokinetics of Sulfobutylether-β-Cyclodextrin in Patients With Varying Degrees of Renal Impairment. J Clin Pharmacol. 2018 Jun;58(6):814-822. https://doi.org/10.1002/jcph.1077 Epub 2018 Mar 26. PMID: 29578585; PMCID: PMC6718009.
10. VEKLURY package insert August 2023, veklury_pi.pdf (gilead.com).

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

BIOGRAPHIES

Dr. Vince Antle is Senior Vice President, QA & Technical Operations, at Ligand, which he joined in 2011 following Ligand's acquisition of CyDex Pharmaceuticals. He is currently responsible for quality assurance, internal drug product quality, operations, distribution, and logistics for Captisol. From 1999 to 2005, he was Technical Operations Manager and Head of Process Development at EaglePicher Pharmaceuticals Services. Prior to 1999, he was the Group Leader for the Combinatorial Chemistry Department of MDS Panlabs in Bothell, WA. He has contributed to publications, presentations, and patents and earned his PhD from the University of Cincinnati in Medicinal Chemistry, and his BA in Chemistry from the University of Minnesota, Morris.



Dr. James Pipkin is Vice President, New Product Development, at Ligand, which he joined in 2011 following Ligand's acquisition of CyDex Pharmaceuticals. His responsibilities include leading internal or assisting clients with development of new applications, intellectual property, and products utilizing CAPTISOL, whether the application involves NMEs, an Orphan designated drug, or reformulations of existing drugs for life cycle management via the 505(b)(2) regulatory pathway. Prior to joining the company, he was Executive Director for CMC Services and Director of Formulation Development at Oread Laboratories from 1995 to 2001. From 1986 through 1995, he was a Research Fellow with Merck Research Laboratories in the INTERx Research Division and West Point PR&D facilities; his area of research interest was in the design and evaluation of controlled release devices for ophthalmic and oral delivery to enhance therapeutic efficacy and lower systemic burden. He has contributed to numerous presentations, publications, and patents and earned his MS and PhD from The University of Kansas in Pharmaceutical Chemistry, and his BA in Mathematics and Chemistry from Kansas University.

Dr. Lian Rajewski is a Senior Investigator at Ligand, which she joined in October 2020. Her current responsibilities include designing and performing analytical and formulation studies to support internal projects, client projects, and intellectual property. Prior to joining Ligand, she was a Research Professor for 11 years at the University of Kansas, Biopharmaceutics Innovation and Optimization Center, where she participated in and managed many formulation, pre-formulation, analytical, and bioanalytical projects, including many development projects involving Captisol. From 2000-2007, Dr. Rajewski held multiple roles at Aptuit its predecessor company, Quinitles, including Director of Solids Formulation Development, Senior Manager, and Senior Scientist. She has contributed to publications and patents and earned her MS and PhD from the University of Kansas in Pharmaceutical Chemistry, and her BS in Pharmacy from the University of Connecticut.

Drug Development
EXECUTIVE

Martin Koeberle, PhD

Head, Analytical Development & Stability Testing

HERMES PHARMA

Bernice Wild, PhD

Head, Stability Testing & Senior QA Manager GCP

HERMES PHARMA

HERMES PHARMA

Get the dose right®

HERMES PHARMA: Reducing Risk, Speeding Development - A CDMO Model Including GCP-Sponsorship to Better Meet the Needs of Pharma Companies

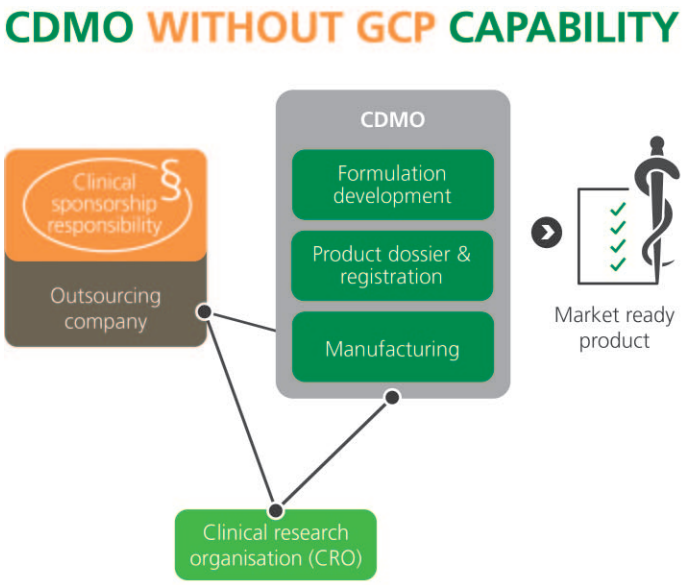
Developing and bringing a new, innovative oral medicinal product to market has always been challenging. To streamline the process, pharmaceutical companies have long sought the expertise and partnership of experienced contract development and manufacturing organizations (CDMOs).

Now, however, the landscape is changing. Pharmaceutical companies are increasingly requesting deeper CDMO support across the whole product development journey. As a result, new service offerings have emerged.

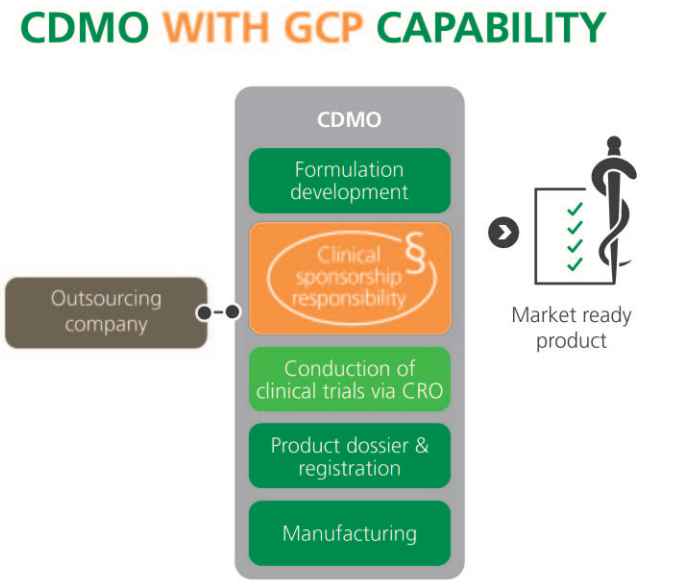
Drug Development & Delivery recently interviewed Dr. Martin Koeberle, Head of Analytical Development & Stability Testing, and Dr. Bernice Wild, Head of Stability Testing and Senior QA Manager GCP, at HERMES PHARMA, to find out more about the challenges of developing innovative oral medicines, as well as how these new service offerings are helping meet a critical need among companies looking to bring portfolio-enhancing formulations to market.

Q: What are the challenges of bringing new, advanced oral medicines to market?

Dr. Koeberle: This task is no easy feat — companies must ensure their new formulation is stable, bioavailable, soluble, and safe, which requires deep expertise and considerable resources. On top of that, it's an inherently risky process with high



The legally required function of **clinical sponsorship responsibility** is with the **outsourcing company**



The legally required function of **clinical sponsorship responsibility** is with the **CDMO**

failure rates, and competition is fierce, so timely development and rapid release to market is critical.

As if that wasn't difficult enough, though, there's growing market pressure for manufacturers to develop more user-friendly oral dosage forms — patient-centric formulations that are easy to swallow, convenient and pleasant to take, and that integrate well into busy modern lifestyles. While user-friendly oral dosage forms offer a wealth of benefits for pharmaceutical companies — deeper brand loyalty, new opportunities to better capture market share, and differentiation in a crowded marketplace — they are inherently more complex to develop and manufacture. For example, they often have more demanding stability and taste-masking considerations, requiring specialist technologies and know-how to get right.

Q: What role do CDMOs play in helping companies overcome such development and manufacturing challenges?

Dr. Koeberle: CDMOs have been — and will continue to be — a critical part of the pharmaceutical development ecosystem, supporting and enabling pharmaceutical organizations of all sizes.

Because CDMOs have such a breadth and depth of expertise, they can often advise on the most efficient routes ahead while foreseeing — and helping avoid — potential stumbling blocks. Ultimately, this translates to more cost- and resource-efficient pharmaceutical product creation.

Importantly, when it comes to time- and resource-strapped pharmaceutical companies, partnering with a CDMO isn't just a benefit, it's often a necessity.

Q: What trends do you see in the CDMO landscape? How are customer demands evolving?

Dr. Koeberle: As noted previously, a larger number of pharmaceutical companies are now turning away from what was once considered the "gold standard" of oral dosage forms — tablets and capsules — to more patient-centric alternatives, such as orally disintegrating granules, effervescent tablets, and instant drinks. After all, around half of people struggle to swallow conventional oral formulations, or just generally find them unpleasant to take. Naturally, that's creating a new space for CDMOs with the expertise to develop and manufacture such user-friendly products.

Critically, at the same time, pharmaceutical companies are more frequently requesting greater support with the clinical aspects of bringing an innovative oral formulation to market.

Q: What makes Good Clinical Practices (GCP) sponsorship such a challenge for pharmaceutical organizations, specifically?

Dr. Wild: While many pharmaceutical companies outsource clinical trials to contract research organizations (CROs), they must still bear the burden of GCP sponsorship. And that comes with a host of responsibilities.

For example, according to ICH Guideline E6(R2), sponsors must have a system in place to manage quality throughout the

clinical study lifecycle. While single tasks can be delegated to CROs as subcontractors, legal responsibility for clinical trial quality and integrity ultimately reside with the sponsor. In practice, that means sponsors must keep on top of a considerable list of duties, including maintaining a Quality Assurance (QA) system with written standard operating procedures (SOPs), ensuring compliance with these SOPs, qualifying contractors, conducting complex audits, serving regulatory GCP inspections, managing deviations and corrective actions and preventive actions (CAPAs), and managing and archiving the considerable documentation associated with that.

Q: How are CDMOs stepping up to meet this growing need?

Dr. Wild: CDMOs with an ear to the ground are aware of this growing need amongst pharmaceutical companies. And a few have stepped up to meet it.

As a result of this growing need, we're now seeing new service offerings emerge needed to bring advanced oral medicinal products to market. This includes GCP sponsorship to perform clinical trials for efficacy or bioequivalence proof. In the end, customers simply buy registrations for the final, successfully developed products, which are ready to be marketed.

Q: What are the benefits of a GCP-capable CDMO for these pharmaceutical organizations?

Dr. Wild: The benefits of this approach are hard to overstate. First and foremost, this type of CDMO offering means customers no longer need to take on the legal responsibility of clinical study oversight required by ICH E6(R2). They therefore don't need to have deep scientific and regulatory knowledge in clinical trials, create and/or maintain a complex QA system, reserve capacity to keep sponsor oversight, and train their staff in clinical trial regulations and requirements.

With a CDMO that has the expertise and ability to handle all aspects along the value chain, customers also get a true "one-stop shop" offering. Working with a one-stop-shop provider simplifies program management for the customer, as they no longer need to liaise with multiple service providers. Because this offering typically shortens drug development timelines, it can also offer a larger, industry-wide benefit — helping to get new medicines to patients more quickly.

Importantly, a CDMO that takes on program-wide responsibility, including shouldering GCP responsibilities and the risk of clinical trials, may have a deeper incentive to ensure product success. For example, customers could get a more targeted formulation development that takes all aspects of product creation into account (including clinical and regulatory considerations), for example.

Customers can reap another benefit too — that of operational efficiency and flexibility. Unburdened by large organization structures and processes they can expect streamlined project management and logistics, and a greater capacity to adapt to changing program requirements. And that could ultimately mean a more cost-efficient and faster time-to-market for your product.

Q: Can these GCP-capable CDMOs help meet the growing need for user-friendly dosage forms too?

Dr. Wild: Absolutely. Some full-service GCP-capable CDMOs specialize in the creation of user-friendly products, using their knowledge in development, manufacture, and testing to deliver market-ready products for pharmaceutical companies to purchase.

A CDMO with deep expertise in, and responsibility for, every step of the creation of user-friendly oral medicines can really de-risk a program by optimizing early steps with later development steps in mind. Take in vitro dissolution assessments and in vivo bioequivalence testing, for instance, which can be particularly challenging in the case of user-friendly oral dosage forms. Knowledgeable full-service CDMOs can maximize chances of study success by carefully tailoring formulation development with those testing requirements in mind (rather than settling for a formulation with good physical and chemical properties alone). Knowledgeable partners can also optimize bioequivalence study strategies in other ways, for example, by selecting the most promising reference product and taking regulatory approaches and constraints into account.

Importantly, the benefits aren't limited to pharmaceutical companies. Yes, such CDMOs unlock a reduced risk, streamlined path to getting user-friendly products into your portfolio. But more importantly, there's a knock-on effect also for patients — with fewer barriers to the creation and commercialization of patient-centric medicines, an ever-greater number of patients can access oral medicines that put them and their needs first. And that's something to celebrate. ◆

In the BioTech Space, You Don't Need
Fun Mascots or Catchy Taglines.

You Need Cutting-Edge Content to Match Your Cutting-Edge Technology.

Modern companies deserve equally advanced marketing strategies. You need an agency that understands the importance of clear, impactful messaging and knows exactly how to navigate the specificities of your industry.

Nicklaus Marketing offers full service marketing solutions for the BioTech industry. That includes video production, comprehensive branding, website design, and digital, and OOH marketing campaigns, all driven by in-depth strategy and research. Everything – from concepting and ideation to execution– through a comprehensive, collaborative process. The end result is impactful work that harnesses the unique power of our clients and their services and technologies.

Your clients don't settle for anything other than the best. Neither should you.

nicklausmarketing.com
info@nicklausmarketing.com
973.538.0450

NICKLAUS
MARKETING & PR

Some of the services we offer.


Industry Events


Web Development


Digital Marketing


Content Development


Sales Tools


Informational Collateral

BIOLOGICS DEVELOPMENT

Five Steps to a Robust Cell Line Development Process

By: Robert Gustines

INTRODUCTION

Biologic production is accelerating, with an increasing number of these essential treatments reaching the market as therapies for a myriad of diseases, including Crohn's disease, hemophilia, diabetes, and cancer.[1] This increasing demand is reflected in the biologics market, which is predicted to expand at a compound annual growth rate of 8.1% to reach $535.5 billion by 2028.[2] As the demand for biologics rises, ensuring robust cell line development is essential.

Working to construct a robust cell line that will lead to efficient, reliable, and reproducible production is the foundation of biologic manufacturing. Cell lines often have distinct associated characteristics that may be beneficial for producing one product but detrimental to another. When deciding between cell lines, each must be carefully considered for the desired biologic to ensure a suitable choice.

Cell line development is the use of various techniques to optimize a cell line for the production of a stable target biotherapeutic in high yield. Not taking the time to implement a robust cell line development process can lead to difficulties down the manufacturing pipeline, which wastes time and increases costs, and could even halt the timeline, as the process may need to be repeated and optimized until the challenges are overcome.

But what steps can be taken to help ease these challenges? The following discusses the critical steps for designing and implementing a robust cell line development process to help overcome the obstacles that often hinder biologic production. By taking the time to understand the cell line, the biologic, and by using advanced synthetic biology techniques to tailor the method to the desired biologic, a proactive approach for robust CLD can be devised.

THE FOUNDATION OF CELL LINE ENGINEERING

Cell line engineering can be challenging, and issues can arise throughout manufacturing. Examples include cell line instability, low yield, low product purity, problems with reproducibility and scalability, or regulatory compliance issues. Fortunately, a number of methods can be adopted to overcome these issues, such as testing various cell lines, generating stable pools, completing extensive and high-throughput screening for clone selection, and using synthetic biology to introduce beneficial characteristics into a cell line. These five techniques, used to generate a robust cell line, are explored in depth further.

1: Choosing the Appropriate Cell Line

Deciding upon the cell line at the earliest possible point is key, as it will impact all subsequent development and manufacturing steps. The conditions for cell growth, expression, and product isolation depend on the selected cell line. As well as impacting factors, such as product quality, quantity, reproducibility, and ef-

ficiency, a robust cell line development platform must also offer scalability. Therefore, it forms the foundation of biologic development and manufacturing.

Many cell line options have been successfully used for biologic development projects. Chinese hamster ovary (CHO) cells are a logical choice, with more than 70% of recombinant proteins produced using this line.[3] With a clear history that sets the basis of documented traceability and ICH compliance, CHO-K-derived cell lines are a safe and easy-to-use option with a track record for gaining regulatory approval. A number of advantages make CHO lines a common choice, including the following:[3]

- Protein folding and post-translational modification processing, such as glycosylation, are closely conserved in nature with human proteins and so are more likely to be accepted by the human system.
- The lines are uniquely tolerant to changes in pH, oxygen levels, pressure, or temperature throughout manufacture, so they can be tailored to the protein at hand.
- The lines are able to grow in serum-free suspension cultures with high cell concentrations, which eases scale-up as it is preferred for large-scale bioreactors.
- There is previous understanding of CHO cell lines with extensive literature available and a regulatory track record, which can help accelerate timelines for approval.

As listed, CHO cells offer several advantages, making them an apt choice. The CHO cell line, however, does have limitations, such as restricted growth and low productivity (when expressing complex artificial molecules), but through genetic engineering, it can be tailored for the desired application.[4]

2: Productivity Improvement Techniques for Genetic Engineering & Non-genetic Optimization of the Cell Line

Biologics are complicated molecules, and past research has shown the CHO cell line may not have the capabilities to produce a particular compound in high yields and at high quality without first being engineered to enhance the expression of the gene of interest to overcome low productivity issue.[5]

Alterations to the core DNA must be completed to impart specific characteristics to the cell line. This is done using genome editing techniques, such as CRISPR Cas, Zinc Finger Nucleases (ZFNs), or Transcription Activator-Like Effector Nucleases (TALENs), to implement specific characteristics.[6] Genetic engineering of the CHO line has been shown to fundamentally alter the function of the molecules expressed.

Biologic expression becomes inherently more difficult as complexity grows. The biopharmaceutical industry is moving toward more intricate molecules, such as next-generation antibodies and protein-based drugs like fusion and multi-specific proteins. However, these revolutionary therapeutics often have lower expression levels in CHO cells as they are artificially designed. While effective for their designed purpose, how these proteins are devised can lead to issues with decreasing solubility and increased aggregation. Engineering can be used to address these issues by introducing the genes for chaperone production (additional proteins that are produced during expression and aid protein folding) into the cell line to help with protein solubility and, in turn, increase product yield. Alternatively, engineering cells to improve the volume of recombinant protein production at low temperatures can also benefit CHO-based expression systems.[7]

Non-genetic cell culture optimization of an existing product-expressing CHO cell line can also improve productivity, for example, by using a low temperature, pH control, media selection, or a feeding strategy. These cell culture process optimizations are synergic to maximize the expression potential of native CHO production cell lines. Different clones have

different responses toward cell culture process changes, and therefore, design of experiment (DoE) is necessary to evaluate multiple CHO cell lines. Developing a scale-down cell culture model representative of at-scale production forms the basis of the DoE.

3: Reducing Variability Between Product Batches

Batch variability leads to unreliable biologic production. Changes in product yield and quality for each batch can result in missed targets and hard-to-predict scales. Variability can be the result of numerous circumstances, from varying growth conditions or materials to cell line composition. Therefore, working to construct a robust cell line and adhering to strict conditions is essential.

Cell line engineering is only made possible by using techniques for efficient transfection and cell enrichment. These high-throughput methods test the viability of an engineered cell line with the product vector to see if the cell engineering has implemented the desired beneficial characteristic (such as increased product yield or solubility) for biologic production.

There are a number of different approaches for inserting the product vector into the target cells, including those based on viral, chemical, and physical transfection for integration. Choosing the best transfection technique for both the vector and cell line is essential to ensure robust vector uptake and limit cell variability.7 Cell enrichment is a method of single cell sorting to isolate positive cells, such as using antibody-based cocktails or flow cytometry.[8] Innovative technologies, such as single-cell printers and high-resolution imagers, make this high-throughput screening possible to ensure monoclonality and increase clone screening efficiency. The method used depends on the application, but for biologic production, a method that leads to high purity is essential.

Optimizing transfection techniques is just one method for limiting variability. An optimized cell line development workflow is also essential; furthermore, a robust single-cell cloning technology minimizes the manufacturing batch-to-batch variability based on the selected clone. Finally, ensuring cell culture medium, growth conditions, extraction techniques, and other production methodologies are meticulously replicated is crucial to reducing variability and ensuring reproducibility.

4: Biologic Analytics Aid Production Viability

Biologic analytics are a powerful tool that can significantly aid the development of stable cell lines. Using intensive biologic analytics early in the cell line development process is essential to fully characterizing and understanding the nature of the biologic. With these characteristics in mind, biologics developers can design production methods knowing the protein will not be harmed by the techniques used during manufacture and that the method is designed to impart stability to the molecule. This circumvents the need for extensive and complex formulations post-production to repair the protein.

Aided by high coordination and free-flowing communication between the analytical and biotechnology groups, this communicative relationship helps to ensure meticulous characterization and top-level visibility, which is especially important for emerging types of molecules (various types of fusion and multi-specific proteins), where less information is known.

5: Scale-up for Market

After extensive optimization and analysis for the reliable production of a biologic, the process then needs to be scaled up to produce enough product for the patient population. Scaling a process up can have unforeseen effects on a biologic and can significantly impact the yield and quality of the product. However, this can be eased by adopting specific intermediary techniques to help aid visibility. For example, using scale-down models to evaluate clones in 50-mL bioreactor spin tubes mimics the larger-scale process so it can be used to predict how a clone will perform within a large-scale bioreactor. Any issues or changes identified when using the 50-mL bioreactor can then be addressed before scaling up to the commercial scale.

As previously discussed, implementing a robust cell line development process helps to reduce batch variability, increase product yield and purity, offer scalability, and reduce production costs. Future risks are also mitigated, and the timeline is less likely to suffer from development and manufacturing delays. However, this can still be very challenging, especially when a highly complex biologic is involved.

A SUPPORTIVE PARTNER AIDS ROBUSTNESS

Working alongside a supportive partner can help ensure a cell line strategy is effective and can aid in maintaining tight timelines. Experienced contract development and manufacturing organizations (CDMOs) have the expertise to help overcome the challenges often encountered at this early stage. They can help with implementing techniques to enhance the stability and productivity of protein drugs for a desired use.

LOOKING TO THE FUTURE

2022 saw a milestone in biologics development: the number of biologic drugs brought to market matched those of new molecular entities (NMEs) for the first time. This growth will only continue, and it is likely biologics will outpace NMEs in the near future.9 A growing understanding of synthetic biology, enhancing our ability to perform complex genetic engineering, facilitates access to increasingly complex and hard-to-work-with biologics to tackle complex diseases.

Therefore, working to implement robust, scalable, and reproducible cell lines at speed is the foundation of biologic production and is essential to keep up with the accelerating biologic market. Investing in new technologies and techniques to streamline CLD will make success more certain and meet customer needs. ◆

REFERENCES

1. Biologics: Types, Treatable Conditions, Mechanisms, Side Effects (verywellhealth.com).
2. Biologics Market Report, Size, Growth and Forecast 2023-2028 (imarcgroup.com).
3. Dumont, J., Euwart, D., Mei, B., Estes, S., & Kshirsagar, R. Human cell lines for biopharmaceutical manufacturing: history, status, and future perspectives, Critical Reviews in Biotechnology, 36:6, 1110-1122, (2016). https://doi.org/10.3109/07388551.2015.1084266.
4. Fischer, S., Handrick, R., & Otte, K. The art of CHO cell engineering: A comprehensive retrospect and future perspectives. Biotechnology Advances, 33:8, 1878–1896, (2015). https://doi:10.1016/j.biotechadv.2015.10.015.
5. Noh, S. M., Sathyamurthy, M. & Lee, G. M. Development of recombinant Chinese hamster ovary cell lines for therapeutic protein production. Current Opinion in Chemical Engineering 2, 391–397 (2013). https://doi.org/10.1016/j.coche.2013.08.002.
6. Dangi, A. K., Sinha, R., Dwivedi, S., Gupta, S. K. & Shukla, P. Cell line techniques and gene editing tools for antibody production: A Review. Frontiers in Pharmacology 9, (2018). https://doi.org/10.3389/fphar.2018.00630.
7. Chong, Z. X., Yeap, S. K. & Ho, W. Y. Transfection types, methods and strategies: A technical review. PeerJ 9, (2021). https://doi.org/10.7717/peerj.11165.
8. Cell Enrichment | SpringerLink.
9. Senior, M. Fresh from the biotech pipeline: fewer approvals, but biologics gain share. Nat Biotechnol 41, 174–182 (2023). https://doi.org/10.1038/s41587-022-01630-6

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

BIOGRAPHY

Robert Gustines is Senior Vice President Commercial Operations at Bora Pharmaceuticals. He has more than 18 years of experience in business development and marketing in the biopharma/pharmaceutical industry. During this time, he has consistently driven revenue and commercial capabilities and enhanced the performance of BD teams in high-growth, proactive, and technology-based environments. He has held several senior roles in Business Development.

FUNCTIONAL EXCIPIENTS

Much More Than Filler: Solving the Challenge of Patient Non-Compliance

By: Carin Siow, PhD

INTRODUCTION

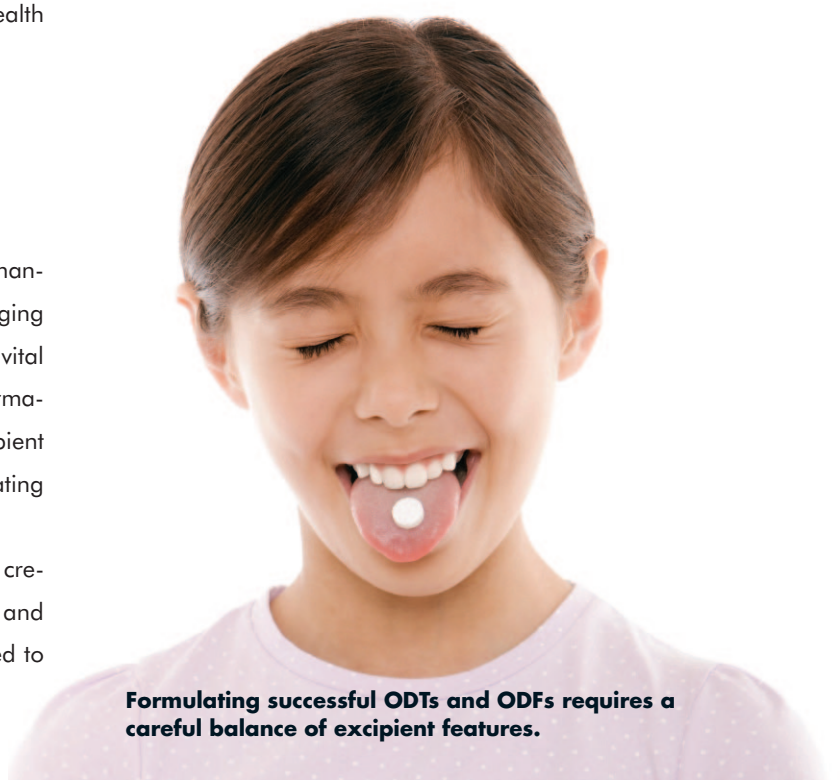
The pharmaceutical industry currently faces one of its toughest challenges to date – the epidemic of patient non-compliance. Recent research suggests medical non-adherence accounts for half of all treatment failures in the US, with serious consequences.[1] This phenomenon is the cause of at least 100,000 preventable deaths and generates unnecessary medical costs of up to $100 billion each year.[2] The stakes could not be higher, yet progress to tackle the root causes of medication misuse has been frustratingly slow. In this article, we want to introduce the pharma industry's secret weapon in the fight against non-compliance – functional excipients. Much more than just fillers that hold tablets together, these ingredients could help manufacturers do their part to turn the tide and drive improved health outcomes for patients around the world.

INNOVATIVE DOSAGE FORMS UNLOCKED

Alongside medical professionals, pharmaceutical drug manufacturers have an equally important role to play in encouraging improved medication adherence. For drug producers, this vital responsibility is usually discussed in the context of active pharmaceutical ingredient (API) efficacy and effectiveness, but excipient selection is just as fundamental a consideration for formulating patient-centric delivery forms.

Choosing the right functional excipient allows brands to create innovative products – from orally disintegrating tablets and films to effervescent and modified-release tablets – designed to meet both patients' medical needs and personal preferences. Ultimately, high-quality excipients make convenient, tailored, and effective dosing methods possible, unlocking new horizons in drug delivery.

Armed with these solutions, pharma manufacturers can reduce medical waste, boost their commercial bottom lines and – most importantly – help patients feel the full benefit of their medications. By taking a closer look at some of the most exciting patient-centric dosage forms available today, it becomes clear just how important functional excipients are for encouraging patient compliance.



Formulating successful ODTs and ODFs requires a careful balance of excipient features.

DEVELOPING ORALLY DISPERSIBLE DRUGS

In any solid dosage form, swallowability, ease of administration, and taste are critical considerations. These factors are imperative for all patient groups, but doubly so for geriatric or pediatric populations, who typically struggle to swallow traditional medications. To address the issues of drug accessibility for patients suffering from dysphagia (difficulty swallowing), formulators have developed a range of disintegrating dosage forms: orally disintegrating tablets (ODTs), orally dispersible mini tablets (ODMTs), and orally disintegrating films (ODFs). Dissolving rapidly when placed on the tongue, these delivery methods simplify the process of taking medication, making it safer, easier, and more convenient for the patient. Because they disintegrate quickly in the oral cavity, taste and overall sensory experience are extremely important. This is where high-quality functional excipients can really add value.

When selecting an excipient for use in ODTs and ODFs, manufacturers must pay close attention to processability, resultant mechanical strength, dispersibility, and palatability. Beyond just checking these features off a list however, balance is a crucial factor in dispersible formulations. This is particularly true when considering mechanical strength and rapid disintegration. While it is important the chosen excipient delivers good strengthening and binding capabilities, this should not hinder the rapid disintegration of the tablet or film. With such a delicate balance to achieve here, multifunctional excipients rapidly become a necessity. Solutions that combine ideal texture properties, with a pleasant flavor and ease of handling allow manufacturers to concentrate on ensuring their ODTs and ODFs can live up to their primary functional advantage – dispersibility.

Based on extensive testing, formulation scientists at Roquette developed PEARLITOL® Flash, a mannitol-starch compound, specifically designed to produce dispersible dosage forms that hit the spot for pharma producers and patients. A direct compression excipient with superior disintegrant properties, PEARLITOL® Flash offers excellent chemical inertness and consistently rapid disintegration time. Additionally, its mild taste and texture make it an ideal choice for swallowable and orally dispersible tablets.

MODIFIED RELEASE, IMPROVED RESULTS

Another significant barrier to patient compliance is pill fatigue. This phenomenon is triggered when patients feel overwhelmed by the number of drugs they must take, something that is more prevalent in geriatric populations who typically require more medications for chronic conditions.[3] For most patients, compliance starts to wane beyond a certain pill count. However, some medications with a relatively short half-life require 2-4 doses daily to be effective. Traditionally, pill fatigue has been characterized as a "patient problem" by medical professionals, without taking into account just how challenging it can be to form the habits required to take multiple daily doses of several different medications.[4] To help bridge the gap between efficacy and patient compliance, pharma formulators are investigating the benefits of reducing dosing frequency through controlled-release dosage forms.

Broadly categorized as extended-release formulations, these dosage forms typically feature a highly soluble BCS (Biopharmaceutical Classification System) Class I or Class III API, combined with a specialized excipient, that slowly release the required amount of drug throughout the day with just one or two doses. Apart from the obvious benefit of reducing dosing frequency, controlled-release drugs offer a host of advantages. By maintaining a more consistent level of medication in the body for example, this delivery method curbs the fluctuations that can cause under

Medical compliance is one of the most pressing issues facing the pharma industry today.

or overdosing, providing therapeutic efficacy with reduced risk of potential side effects. In recent years, producers have also begun to extend the benefits of gradual release formats beyond the realm of oral dosage forms. Multiple-day transdermal and subcutaneous depot formulations administered via transdermal microneedle patches, for instance, offer an effective, painless method for overcoming the GI barrier when delivering large molecule biologics. They are therefore gaining popularity as an alternative to traditional multi-dose oral regimens. Such features may result in improved bioavailability, safety, and effectiveness, as well as better patient compliance.

Getting down to practicalities, successful modified drug development hinges on selecting a polymeric-based excipient, capable of allowing the API to be gradually diffused from the tablet. Typically, these excipients, such as hydroxypropyl methylcellulose (HPMC), work by forming a gel-like matrix when they come into contact with the aqueous environment of the GI tract. This feature ensures the active ingredient takes longer to diffuse out of the tablet, resulting in a slower drug-release profile. In addition to the excipient type, manufacturers must also consider the proportion needed to achieve the desired rate of drug release at the absorption or target site.

To complement the effect of these slow-release ingredients, Roquette offers a broad range of directly compressible excipients, such as magnesium stearate and MICROCEL® microcrystalline cellulose, which exhibit good flow and compaction properties to help formulators develop successful controlled-release drugs. The superior stability exhibited by Roquette excipients offers another advantage – helping to ensure both reproducibility and reliability so patients experience the same outcome after each and every dose.

THE "SOFTER" SIDE OF DRUG DELIVERY

While delivery methods tend to dominate the conversation surrounding patient compliance, smart excipient solutions can go further than just addressing dosage preferences. By aligning their solutions with people's values and ideals, as well as their physical needs, drug producers can ensure patients are not only capable of

taking their medication but are actually comfortable doing so.

Take the rising demand for plant-based healthcare solutions as an example. The number of people following vegetarian and vegan diets, or simply seeking to consume fewer animal-derived products, has skyrocketed in recent years.[5] As such, the widely popular softgel capsule format faces a serious issue. Due to its multifaceted functional properties and natural positioning, gelatin has historically been the excipient of choice for these applications. But with its origins as a byproduct of the meat industry, this well-known ingredient is unsuitable for veggie or vegan-friendly drug development.

Again, innovative excipients can circumvent this problem by providing brands with new opportunities to create pharma and nutraceutical products powered by plant-based materials. First-of-a-kind pea starch technologies, like Roquette's LYCAGEL® plant-based softgel solution, give brands the option to develop vegetarian softgels that perform equally, if not better, than gelatin-based solutions, while still adhering to the stringent quality standards required in the highly regulated pharmaceutical and nutraceutical markets. Higher performing and more sustainable than other gelatin-alternatives, these plant-based solutions deliver transparent, shiny capsules with a neutral taste that are easy for patients to swallow – both literally and metaphorically.

IT ALL COMES BACK TO PEOPLE

In these technical discussions on polymer matrices, dispersibility, and optimal API delivery, it can be easy to forget the people at the center of the patient-compliance issue. Medical noncompliance is one of the most pressing issues facing the pharma industry today, but it is even more serious for patients who are not receiving the treatments they need, want, or deserve. Ultimately, optimal medication lies in the intersection of efficacy and effectiveness – wherein efficacy refers to the ability to cause a therapeutic effect and effectiveness relates to its value in real-world use.[6] A general rule of thumb is that drugs tend to score lower on effectiveness than efficacy because clinicians prioritize short-term discomfort over long-term health benefits.[7] But to achieve truly ideal drug delivery, manufacturers should strive to redress the balance and put patient experience on a par with a medication's baseline efficacy.

As the range of excipients available to pharma brands increases, so do the opportunities to tackle this challenge with smart drug delivery. Game-changing APIs are undoubtedly important for improving user acceptance, but innovative excipients also deserve a place in the patient compliance conversation. A trusted excipient supplier therefore has an extremely important role to play in helping pharmaceutical manufacturers solve their formulation and delivery challenges. Much like the process of combining the right API, excipient, filler, or binder – ingredients suppliers, pharma producers, clinicians, and patients can overcome these challenges by combining forces and working together to build a healthier future for all. ◆

® Registered trademarks of Roquette Frères.

REFERENCES

1. Elephant in the Room, US Pharm. 2018;43(1)30-34, https://www.uspharmacist.com/article/medication-adherence-the-elephant-in-the-room.
2. Kleinsinger F. The Unmet Challenge of Medication Nonadherence. Perm J. 2018;22:18-033. doi: 10.7812/TPP/18-033. PMID: 30005722; PMCID: PMC6045499.
3. Keppel Health Review, Pill fatigue, 25 February 2022, https://www.keppelhealthreview.com/winter2022/pillfatigue#:~:text=Pill%20fatigue%20is%20when%20a,they%20have%20to%20take%20them.
4. Ibid, Kleinsinger F.
5. Food Revolution Network, Why the Global Rise in Vegan and Plant-Based Eating is No Fad (30x Increase in US Vegans + Other Astounding Vegan Stats), 6 April 2022, https://foodrevolution.org/blog/vegan-statistics-global/.
6. Shalini S. Lynch, MSD Manual, Drug Efficacy and Safety, last reviewed May 2022, https://www.msdmanuals.com/en-gb/professional/clinical-pharmacology/concepts-in-pharmacotherapy/drug-efficacy-and-safety.
7. Ibid, MSD Manual.

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

BIOGRAPHY

Dr. Carin Siow is a Senior Pharmaceutical Application Scientist at the Roquette Applications Lab. She earned her Bachelor's degree in Pharmacy and her PhD in Pharmaceutical Technology from National University of Singapore. As a registered pharmacist, she is passionate about leveraging the advantages of excipients to improve the design of dosage forms for patients. Her current role involves working on application studies and developing technical materials to broaden the formulation and processing understanding of the Roquette excipient portfolio.

PRIMARY CONTAINER CLOSURE SYSTEMS

In From the Cold: Realizing the Benefits of Primary Packaging Innovation for Lyophilized Drug Products

By: Neal Higgins

INTRODUCTION

Many in the pharmaceutical industry are well aware of the benefits of lyophilization (or freeze-drying) in ensuring the stability of certain formulations, such as proteins, monoclonal antibodies, enzymes, and vaccines.

The market also understands some of the challenges associated with lyophilization in terms of maintaining quality; namely mitigating against particulates and ensuring container closure integrity (CCI). There are challenges too in terms of managing operational efficiency and mitigating costly downtime.

The following will quickly revisit the benefits and challenges associated with lyophilization before reviewing some of the current macro influences, including the EU GMP Annex 1 revision. It will then discuss West's design philosophy and Quality-by-Design (QBD) blueprint, before showcasing its 4040 LyoTec® Stoppers, which help mitigate the compromises associated with the current marketed products. Finally, it will showcase data to demonstrate the efficacy of the 4040 elastomer platform.

LYOPHILIZATION – THE COMPLEXITIES & BENEFITS

There are myriad threats to a drug's stability and integrity over time, and each of these threats has the potential to compromise the desired therapeutic effect and therefore the intended outcome for the patient.

Moisture is a case in point. There are some pharmaceutical substances, including proteins, monoclonal antibodies, enzymes, and vaccines, in which the solution state required for parenteral administration can itself be a catalyst for degradation through enzymatic or hydrolytic reactions. In these circumstances, the process of lyophilization, or freeze-drying, allows stability to be maintained by altering the state of the drug from a fluid to a dry powder, causing metabolic processes to halt.

Lyophilization in simple terms describes the removal of water, but the process is undoubtedly highly complex and time-intensive, with three critical stages involved: freezing, sublimation (primary drying) and desorption (secondary drying).[1] In its resultant freeze-dried cake form, the drug is more stable, meaning formulations benefit from a longer shelf- life and are easy to transport. When it then comes to administration, healthcare professionals are tasked with reconstituting the powder with a sterile diluent to form

4040 LyoTec® Stoppers: Comprised of a State-of-the-Art Elastomer – Advancing Quality & Manufacturability

an injectable solution.

Because the benefits of lyophilization are contingent on the sustained absence of water, drugs in a dry-powder state present particular challenges in terms of being contained within a secure, low-moisture environment. Indeed, the Ancient Greek roots of the word lyophilization, which loosely translated means a love of dissolving, underline the inherently absorbent properties of the drug in this form and the ever-present risk of the stability of the lyophilized drug product being compromised through contact with moisture.[2]

PACKAGING MUST BE A PRIMARY CONSIDERATION

In this context, the choice of primary packaging components is crucial. Together, all elements must harmoniously contribute to safeguarding the drug product in dried form during manufacturing, transportation, and storage. The elastomer stopper, which fulfills the role of sealing the vial's contents against the external environment, demands particular attention. This interface presents several theoretical moisture-related risks. This includes the potential to release residual moisture contained within the stopper itself, as well as its potential to facilitate permeation of water from the environment, both as a direct conduit and via the interface between stopper and vial.

With these risks in mind, an understanding of the independent physico-chemical attributes of vial and stopper, and the interplay between these two elements, is critical in achieving the containment properties necessary to maintain lyophilized drugs in their desiccated state.

One of the many critical quality attributes (CQAs) for stoppers in lyophilization applications is the Moisture Vapor Transmission Rate (MVTR). This value must be recorded at a low level to ensure the elastomer does not encourage the transfer of atmospheric water.

Furthermore, there must also be consideration of treatments the component will undergo during processing. This includes steam sterilization carried out in an autoclave, which involves moisture being absorbed by the stopper and removed via a drying process. It is essential this final stage is optimized in "Goldilocks" conditions of no more than 8 hours and at a temperature no higher than 105°C – a criteria "just right" to sufficiently reduce moisture levels but avoid the elastomer being over-exposed to conditions that can result in degradation. It's important to note the exact parameters for sterilization and drying will influence the resulting water content. For example, the drying cycle will need to factor in the physicochemical properties of the elastomer and the performance and efficiency of the autoclave chamber.

Dimensional fit between stopper and vial is also critical to the effective containment of a lyophilized drug product. Vials are subject to a staged sealing process, and CCI can be threatened if the stopper becomes displaced at any point through pop-up. Pop-up describes the scenario in which the edge of the stopper, or the entire component, is raised above the top of the vial following stoppering, introducing the risk of contamination and exposure to moisture.

In lyophilization, stoppers are initially inserted partially into the vial opening following aseptic filling to provide the vent that allows for sublimation during the lyophilization process. The stopper must remain secure in this position throughout the freeze-drying process until the lyophilizer shelves are lowered to fully seat the stopper in the vial. It must continue to remain fully seated during transportation from the lyophilization chamber to the crimping station, where the long-term seal is achieved.

Pop-up can be driven by many factors, including when the plug diameter of the stopper is too big and there is a resulting increase in the insertion force required to seat the stopper accurately. It can also be triggered during the lyophilization process when stoppers stick to the lyo shelves of the lyophilization chamber at the point they are raised. This

adhesion can lead to the stopper being improperly seated, impacting CCI prior to capping. Ultimately, it can result in drug spills within the lyophilizer, with costly wasted drug product, production downtime, and the need to undertake clean-up procedures.

It is clear then that all attributes of a primary packaging system must combine to form an uncompromisingly secure environment; one that not only protects the lyophilized drug product itself, but also consistently mitigates the risk of contamination by particulates, safeguards sterility, and mitigates potential risk to patient safety.

DON'T FREEZE UNDER THE PRESSURE OF EU GMP ANNEX 1

In recent years, regulatory authorities have implemented changes to drug manufacturing regulations with a view to enforcing these objectives. Most recently, in August 2022, the European Commission published the final revised version of EU GMP Annex 1 relating to the Manufacture of Sterile Medicinal Products for human and veterinary use. The updated Annex 1 is scheduled to come into force on August 25, 2023, (with the specific exception of Chapter 8.123, which relates to product transfer for lyophilizers and takes effect from August 25, 2024).[3]

The updated guidance remains faithful to the original structure of Annex 1, but goes into far greater depth in certain areas, as well as introducing the requirement to implement a Contamination Control Strategy. Patient safety might be at the root of this change, but it also addresses the fact that particulates and sterility are a major cause for costly product recalls.

Despite the current focus on EU Annex 1, the European Union is not the only territory where the bar of expectation is being raised when it comes to regulatory standards for particulates. The pharmacopeia of the US, Japan, and China also place emphasis on the eradication of visible foreign matter, and updates to risk management and compliance guidance in recent years point to an underlying ambition among regulators to manifest a future essentially free from particles. Indeed, on average, 34% of FDA recalls for approved injectable products were attributed to issues with foreign particulates or a lack of sterility that stemmed from the container closure being sub-optimal.[4,5]

WEST'S QUALITY-BY-DESIGN PHILOSOPHY

At West Pharmaceutical Services, we translate challenges around improving contamination control and maintaining drug product stability into strategic objectives. To our organization, they form the starting point for the development of innovative components and systems designed with the future in mind, ensuring our pharmaceutical partners are equipped with solutions that fit into their current supply chains and workflows, while meeting the ever-more stringent demands of the evolving regulatory landscape.

A case in point is West 4040 LyoTec vial stoppers, which have been developed directly in response to the CCI risks and processing challenges pharmaceutical partners are facing for lyophilized drug products. This platform was realized through the principles of QbD, using a systematic, science-based approach to meet highly targeted market-driven objectives. Not only are product features designed to meet Quality Target Product Profile (QTPP) goals, there is also consideration of performance within manufacturing environments. This all-encompassing approach provides a platform for the mitigation of development risk, ensuring variables are closely controlled, choices are backed by robust data, and the resulting innovation delivers the impact expected without compromise.

West's continued use of QbD principles mean the properties of the 4040 LyoTec stopper, from the raw materials to the milling and compounding processes, are collectively focused on reducing the extractables and leachables (E&L) profile as well as addressing risks associated with fragmentation/coring and particulates, which are further mitigated through a validated wash process. The product is engineered to a tighter moisture-specification standard and, aligned to our emphasis on data, every batch is analyzed and certified, with particulate levels shown to be consistently low and warranted to the Westar™ Select process specifications for our high-quality, industry-proven stoppers.

Extensive consideration has also been given to how the stopper can be integrated into global supply chains. For this reason, West's 4040 LyoTec stoppers are designed to be universally compatible with European blow back, no blow back, and American blow back ISO glass vial types in 13-mm and 20-mm formats.

To verify this compatibility, helium leak CCI testing was performed across all formats using 4040 LyoTec stoppers in conjunction with ISO 2R and 10R tubular vials. For both non-aged stoppers and stoppers aged in ambient conditions, across all vial types, the tested containers exceeded the minimum Kirsch Limit requirement for CCI of $6x10^{-6}$ mbar L/s.

While this compatibility between vial and stopper is, of course, fundamental to maintaining the integrity of the drug product, the stopper must also be considered in the context of manufacturability.

As such, the 4040 LyoTec stopper incorporates optimized drying properties to improve steam sterilization and its igloo design is proven to be effective at limiting the disruption caused by stoppers joining together, or twinning, in the feeder bowl. This risk is further reduced, along with risks of clumping and sticking, due to the stopper's B2-Coating, which provides a low-particle alternative to conventional silicone oil. Additional benefits are also realized through the incorporation of FluroTec™ film on the top surface of the stopper closure, which has been shown to play an integral role in reducing adhesion to the lyo shelves.

Finally, to assess the risk of pop-up, oxygen-headspace analysis has been conducted using vials of all blowback geometries. These tests confirmed the 4040 LyoTec stoppers maintained CCI without capping for 24 hours in all formats of the vials tested.

Taken together, the combined results of all these tests illuminate how the 4040 LyoTec stoppers can be seen to tackle major factors behind compromised CCI while also avoiding manufacturing downtime by reducing instances in which drug product is lost and clean-up procedures hamper production efficiency and jeopardize employee safety.

To provide a complete system for assured CCI and efficient manufacturability, West can also combine 4040 LyoTec stoppers with Corning® Valor® Glass vials from Corning Incorporated. Compared to conventional vials, the Valor Glass product significantly reduces the risk of damage and breakage during low temperature processes, such as lyophilization, delivering benefits for productivity and employee safety. This is the result of a chemical strengthening process that imparts compressive stress on the glass surface to levels that typically exceed the tensile stresses generated during the freezing or ice nucleation processes. A low coefficient of friction (COF) coating is applied to the exterior of the containers, improving damage resistance, machinability, and reducing particulate generation. Such properties not only offer enhanced protection for high-value drugs, but they may also allow for more aggressive and faster lyophilization cycles in some cases.

SUMMARY

Upon reflection, the fact these various manufacturability and containment challenges need to be overcome at all provides evidence of the complexity involved in lyophilization. However, in a market where moisture-intolerant biologics and more complex therapies continue to grow in share, the ability to transform parenteral solutions into dry powders remains a potent weapon against destabilization and degradation.

For pharmaceutical companies, the future of lyophilization will therefore continue to be defined by assurances of CCI and the need to control contamination in the face of increased regulatory oversight. Armed with world-class product innovation that draws on QbD principles, West has shown how it is possible to source components that answer lyophilization's short-term challenges while providing a pathway to satisfy the functionality, performance, and safety demands of tomorrow. ◆

REFERENCES

1. https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-guides/lyophilization-parenteral-793.
2. https://link.springer.com/book/10.1007/978-1-4939-2383-0.
3. https://www.gmp-compliance.org/gmp-news/finalised-the-revised-eu-annex-1-is-published.
4. https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/recalls-biologics, accessed February 14, 2023.
5. https://www.fda.gov/drugs/drug-safety-and-availability/drug-recalls, accessed February 14, 2023.

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

BIOGRAPHY

Neal Higgins is a Consultant Program Manager at West Pharmaceutical Services. One of his many roles is to assist customers in process-related activities involving West products. He is also a member of the Purdue University LyoHub, an industry-focused consortium to advance the science and technology of lyophilization. He has spent 30 years in the pharmaceutical industry, where he held various SME and leadership roles in Parenteral Fill/Finish Operations as well as Delivery Device Research & Development. At the time of his retirement from Eli Lilly in 2017, he was the Global R&D System Lead Engineer for all vial systems. His broad range of knowledge and experience in aseptic processing combined his knowledge of primary container closure systems provides valuable insights and solutions for customers.

PLACENTA-ON-A-CHIP

The Future of Drug Discovery In Women's Health

By: Hagar Labouta, PhD

INTRODUCTION

Pregnancy presents many challenges when it comes to drug development. Biological changes that a woman experiences between conception and delivery may alter the way medications are absorbed, transported, and metabolized, and certain drugs may cross the placental barrier, affecting fetal health.[1] Concerns for the health of the mother and fetus have limited clinical studies in pregnant populations, so investigations into the effects of therapeutic agents during pregnancy have been virtually non-existent for decades. However, a lack of knowledge about antenatal care is also dangerous, as the vast majority of pregnant women today experience health concerns that require treatment, and often have to resort to taking unapproved medications during gestation. In addition, obstetric complications – many of which are preventable or treatable – still threaten the lives of many mothers and babies worldwide, due to a lack of research into the management of these conditions. Today, scientists are seeking innovative methods to model the physiology and pharmacology of human pregnancy. The following article will discuss the current challenges that face pregnancy therapeutics, new opportunities the field of microfluidics offers for obstetric research, and how one Canadian research group – the Labouta Laboratory – is pioneering nanotechnology drug delivery models for the safe and effective treatment of antenatal conditions.

MATERNAL HEALTH & DISEASE

The physiological effects of pregnancy are extensive, affecting almost every bodily system over the course of 39 weeks. In addition to hormonal variations, an increase in blood volume and a developing fetus, more obvious changes to a woman's body include the expansion of the uterus – the hollow, muscular organ that supports the fetus – and the formation of the placenta in the first trimester.[2]

The placenta is a temporary, dynamic, and highly specialized organ attached to the wall of the uterus that plays an important role in facilitating nutrient and oxygen exchange, protecting the fetus from harmful substances in the maternal circulation, and producing hormones to support fetal development.[3] Additionally, the placenta is known to play an important role in health and disease, providing immunity to the growing fetus by acting as a barrier to protect it from infections and other maternal disorders that can occur at any stage of pregnancy. Some of the most common of these health concerns are high blood pressure, gestational diabetes, pre-eclampsia, preterm labor, and miscarriage and, although the placenta can – to some extent – protect the fetus from these effects, medical management of disease during pregnancy is still essential.

TREATING FOR TWO

More than half of pregnant women currently take prescription medications or over-the-counter drugs at some point during gestation to control pre-existing illnesses or acute conditions.[4] In fact, the use of pharmaceuticals during pregnancy is on the rise, partly because of advancing maternal age, as well as the growing incidence of long-term health conditions that require ongoing therapy even before women conceive. The majority of these medications appear to have little to no effect on the fetus, indicating it is possible to have a long and healthy pregnancy while medically managing maternal health. However, ethical issues surrounding the inclusion of pregnant women in clinical trials, as well as regulatory concerns about drug development for maternal

and fetal conditions, means many drugs have never been directly studied in the context of pregnancy.[1]

BARRIERS TO RESEARCH

Many factors need to be taken into account to carry out effective pharmacological studies while prioritizing fetal and maternal health. The abundance of physical and physiological changes that occur during gestation can influence pharmacokinetics – the way in which a person's body handles an administered drug, distributing and eliminating it from the body. This can affect how well the medicine works, and doses that are therapeutic in the non-pregnant state may have to be modified to achieve the required therapeutic levels in pregnancy. An additional consideration when treating pregnant women is potential adverse effects of drugs on the developing fetus. Congenital malformations occur in between 2% and 3% of newborn babies worldwide, with approximately 1% to 2% of this total being due to teratogenicity – the presence of certain harmful substances in medicines that can breach the placental barrier and impact normal fetal development, alter the placenta itself, or modify a pregnant woman's physiology, harming the fetus indirectly.[5,6]

The potential risks of treating diseases during pregnancy, combined with ongoing controversies around the inclusion of pregnant women in clinical research, necessitate a complete shift in the way that we study pregnancy therapeutics. Researchers are therefore focusing their efforts on designing a model that effectively recapitulates the human pregnancy, so that drug testing can be carried out *in vitro*, without risks to the mother or fetus.

Researchers from the Labouta Laboratory are seeking innovative methods to treat maternal diseases and congenital fetal disorders.

REPLICATING THE PRENATAL ENVIRONMENT

Establishing an efficient replica of obstetric physiology and pharmacology is a difficult task. Human pregnancy is a unique phenomenon; women experience a longer gestation period – even when body size is adjusted for – as well as a drawn-out labor and delivery process compared to many other animals.[7] In addition, adverse pregnancy outcomes, like preterm birth and pre-eclampsia, are much more common in humans than other species. Although a number of animal models have been proposed for use in pregnancy studies, including small primates and mouse models, they typically have poor physiological relevance to human gestation, offering weak predictive power and typically requiring genetic modification in order to study human diseases.[8] Another model, which has historically been used to study placental function in response to therapies, uses end-of-term human placental tissue that is discarded after delivery. However, even *ex vivo* models based directly on the human placenta are not truly representative of the fluctuating nature of this complex organ, which changes significantly in terms of both structure and function between the first and third trimesters.

Motivated by the challenges of existing models, scientists are now implementing new and advanced technologies to replicate human pregnancy and enhance empirical knowledge in this field. One research group, based in the Labouta Laboratory, has pioneered the use of microfluidics technologies – the manipulation of fluids in small volumes – to design a novel model of the human placenta. This lab-on-a-chip model relies on a microfluidic cell culture device containing tiny microchannels inhabited by living cells, which are arranged carefully to replicate tissue- and organ-level physiology.[9] The technology has allowed researchers at the university to culture placental cells and matrices, creating a dynamic model that enables investigations into how therapeutics interact with the placental barrier. The team is using this model to develop and test safe and effective nanoparticle-based therapies to treat obstetric complications.

STUDYING PREGNANCY PHARMACOLOGY

Effective nanoparticle drug delivery has already been demonstrated for the treatment of widespread infectious diseases and cancers, in which nanoparticles – engineered particles on the nanometer scale – have been successfully exploited to load, carry, and deliver drugs to the required tissues.[10] Applying these treatment methodologies in the field of obstetrics opens up new avenues for treating pregnancy-associated diseases with minimal off-target effects, because nanoparticles can be engineered to deliver drugs selectively to an organ with precise dosages, controlled release, and reduced side effects. Using another custom microfluidics system from Dolomite Microfluidics, the Labouta Laboratory is applying nanotechnology to deliver microRNAs to modelled placental tissue, enabling research into the effects of different formulations on both maternal and fetal tissues.

The placenta-on-a-chip model will allow researchers to develop a better understanding of placental function, including how nanoparticles interact with the various cellular layers of this barrier under both physiological and pathological conditions. As research progresses, this will enable selective development of drugs that target the fetus, as well as medications that cannot cross the placental barrier, depending on the aim of the project. For example, when developing a medication to treat congenital conditions, it is important that therapeutic substances can travel through the mother's bloodstream and cross the placenta to reach the fetus. On the other hand, it is crucial that nanoparticles targeted at placental tissues or neighboring cells – to treat maternal conditions such as pre-eclampsia – have therapeutic effects on maternal physiology without transferring through the placenta or adversely affecting fetal tissues.

DEVELOPING SAFER PREGNANCY THERAPEUTICS

The main focus of the laboratory's current work is developing an effective treatment for congenital diaphragmatic hernia (CDH), a birth defect of the diaphragm. Most congenital abnormalities are considered rare, but CDH is one of the most common of these conditions – occurring in as many as 1 in every 2,500 live births – with potentially serious outcomes, including death shortly after birth or lifelong respiratory issues that require resource-intensive surveillance and medical care.[11] Until now, there has been no available cure for this serious prenatal abnormality, but the team in the Labouta Laboratory is using microfluidic technologies from Dolomite to design novel therapeutic microRNA-loaded lipid nanoparticles to treat the developing fetus in the mother's womb.

Although microfluidics is a fairly new approach to drug development, it is already considered the gold standard technique for RNA delivery, lending many benefits to the treatment of CDH. This technology enables the production of small, lipid-based vesicles to deliver therapeutic RNA directly to the impaired fetal respiratory tract. Encapsulating microRNAs within purposely formulated lipid nanoparticles offers the potential for more controlled and sustained release, while reducing toxicity and minimizing adverse side effects. In addition, downsizing particles to the nanometric scale reduces the volume of reagents needed during drug delivery, making microfluidics a cost- and resource-efficient way for the laboratory to investigate novel treatments for conditions like CDH that, until now, have remained poorly understood.

A FORWARD-THINKING APPROACH

It is essential that adequate and consistent information is available to expectant mothers about pregnancy complications and new and existing medications, so that they can make informed decisions to optimize pregnancy outcomes. Given the potential risks of includ-

The Labouta Laboratory is using microfluidics technologies from Dolomite Microfluidics to develop nanoparticles that improve the outcomes of diseases like CDH.

ing pregnant women in *in vivo* human studies, and the limitations of existing placental models, microfluidics offers a safer, more effective, and increasingly adaptive methodology for modelling pregnancy pharmacology. Researchers in the Labouta Laboratory continue to increase the complexity of their placenta-on-a-chip models and, as their research progresses, they are confident this technology will aid the development of novel therapies to treat a wide range of maternal and fetal conditions. The rapidly growing field of microfluidics therefore has the potential to completely transform the prenatal drug development landscape and improve the availability of pregnancy-approved medications to women across the globe.

SUMMARY

The development of medicines to treat maternal and fetal conditions has historically been limited by a lack of knowledge of pregnancy physiology and pharmacokinetics, combined with ethical and regulatory concerns regarding the inclusion of pregnant populations in clinical trials. Microfluidics technologies offer significant potential to the field of pregnancy therapeutics, because nanoparticles can be engineered to minimize fetal drug exposure when required, and deliver therapies safely to intended tissues. Similarly, placenta-on-a-chip technology offers high potential for testing the antenatal safety of therapeutics. Researchers in the Labouta Laboratory are developing increasingly complex microfluidics models of the placenta, and these studies have the potential to improve both maternal and fetal survival rates – as well as quality of life after birth – providing novel and exciting opportunities to an area of research that has long been overlooked. ◆

REFERENCES

1. David, A.L. et al. 2022. Improving development of drug treatments for pregnant women and the fetus. Therapeutic Innovation & Regulatory Science, 56(6):976–990. doi: 10.1007/s43441-022-00433-w.
2. Pascual, Z.N. and Langaker, M.D. 2023. Physiology, Pregnancy. StatPearls Publishing. Available at: https://www.ncbi.nlm.nih.gov/books/NBK559304/.
3. Weinberg, D.H. 2022. Human placenta project, Eunice Kennedy Shriver National Institute of Child Health and Human Development. U.S. Department of Health and Human Services. Available at: https://www.nichd.nih.gov/research/supported/human-placenta-project/default.
4. Gunatilake, R. and Patil, A.S. 2023. Drug use during pregnancy, MSD Manual Consumer Version. MSD Manuals. Available at: https://www.msdmanuals.com/home/women-s-health-issues/drug-use-during-pregnancy/drug-use-during-pregnancy.
5. Leung, C. et al. 2022. Principles of drug use and management in pregnancy. Pharmaceutical Journal, 309(7963). doi: 10.1211/pj.2022.1.150391.
6. Tetro, N. et al. 2018. The placental barrier: The Gate and the fate in drug distribution. Pharmaceutical Research, 35(4). doi: 10.1007/s11095-017-2286-0.
7. Mika, K. et al. 2021. Evolutionary transcriptomics implicates new genes and pathways in human pregnancy and adverse pregnancy outcomes. eLife, 10. doi: 10.7554/elife.69584.
8. Carter, A.M. 2020. Animal models of human pregnancy and placentation: Alternatives to the mouse. Reproduction, 160(6). doi: 10.1530/rep-20-0354.
9. Bhatia, S.N. and Ingber, D.E. 2014. Microfluidic organs-on-chips. Nature Biotechnology, 32(8):760–772. doi: 10.1038/nbt.2989.
10. Pritchard, N. et al. 2020. Nanoparticles in pregnancy: The next frontier in Reproductive Therapeutics. Human Reproduction Update, 27(2):280–304. doi: 10.1093/humupd/dmaa049.
11. The Children's Hospital of Philadelphia. 2014. Congenital diaphragmatic hernia (CDH). Available at: https://www.chop.edu/conditions-diseases/congenital-diaphragmatic-hernia-cdh.

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

BIOGRAPHY

Dr. Hagar Labouta is the Keenan Research Chair of Nanomedicine at Unity Health Toronto, and an Assistant Professor in the Leslie Dan Faculty of Pharmacy at the University of Toronto. Previously, her laboratory was affiliated with the College of Pharmacy at the University of Manitoba. She has extensive research experience in the areas of nanomedicine, drug delivery, and biomedical engineering, as well as a strong publication record, and is a co-inventor of an international patent for the development of carrier systems for intracellular drug targeting. She earned her PhD in Pharmaceutical Nanotechnology at Saarland University in Germany under the supervision of Professor Marc Schneider, followed by post-doctoral research under the supervision of Professor Claus-Michael Lehr in the Drug Delivery Department at the Helmholtz Institute for Pharmaceutical Research. After emigrating to Canada, she continued her post-doctoral studies at the University of Calgary, where she focused on other areas of nanomedicine in the Departments of Chemistry and Biomedical Engineering, under the supervision of Professors David Cramb and Kristina Rinker, respectively. The Labouta Laboratory is supported by several local, national, and international funds.

DELIVERY TECHNOLOGY

Topical NeuroDirect™ Ketamine in the Treatment of Neuropathic Pain Syndromes: Fibromyalgia, Neuropathy, Radiculopathy & Causalgia/ Complex Regional Pain Syndrome

By: Ronald Aung-Din, MD, and Chantelle Martin, MBChB

NEUROPATHIC PAIN INTRODUCTION

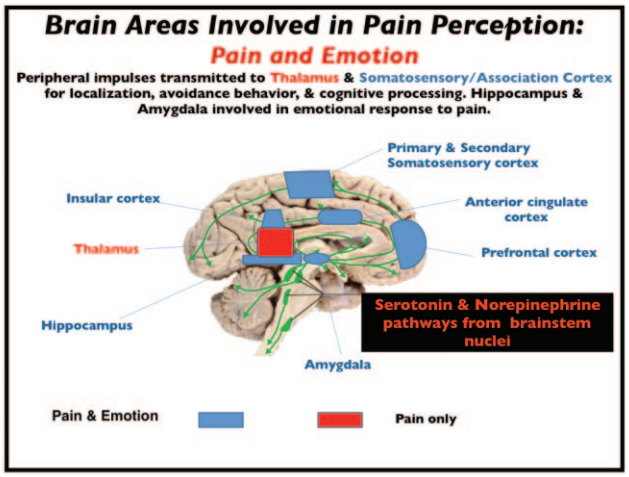
Pain can be classified as nociceptive and transient; or, neuropathic and chronic.[1] Nociceptive pain alerts of acute injury; and generally resolves after injury heals. Neuropathic pain, on the other hand, serves no physiologic purpose. It is the result of aberrant pain impulses relaying to central nervous system (CNS) from prior peripheral injury. It is chronic, unrelenting, and affects function and mood. Described in such terms as "burning, aching, electric-like, and constant," it involves several different areas of CNS. (Figure 1).

Figure 1 illustrates different areas of CNS affected in chronic neuropathic pain. Primary and secondary somatosensory cortices are involved, as well as areas subserving emotion, memory, and reward behavior. Neuropathic pain affects both physical and psychological aspects of human function.

With causalgia or complex regional pain syndrome, CRPS, up-regulated CNS structures cause spread of pain and vasomotor symptoms to parts other than the primary site of injury.

In fibromyalgia, the causative factor may be a remote traumatic event, separated in time, sometimes years, from events which later contribute to "total body pain," the hallmark of the disorder. The initial event may be tied to emotional or physical abuse, or both; which remains embedded and unresolved in an individual's psycho-social being. Later, an injury, seemingly trivial, causes the "dam to break" with body-wide symptoms of pain,

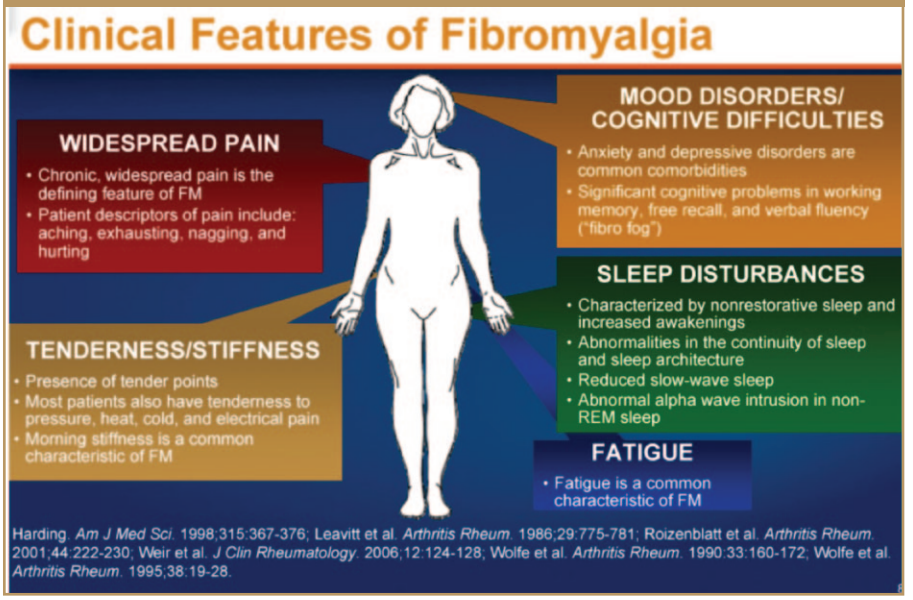
FIGURE 1



stiffness, and weakness. Other symptoms that frequently accompany are depression, anxiety, mood swings, sleep loss, and chronic fatigue.[2,3]

Pain serves to alert of injury; left neglected, brain structures involved with pain perception up-regulate, resulting in heightened perception and other associated symptoms. Emotional pain increases such up-regulation more than physical pain. Both are influenced by norepinephrine, NE, and serotonin, 5-HT. In a heightened emotional state, physical pain is more acutely perceived; alternatively severe physical pain affects mood.

FIGURE 2



KETAMINE & THE NMDA RECEPTOR IN NEUROPATHIC PAIN

There has been much attention on the N-methyl-D-aspartate, NMDA, receptor antagonist, ketamine, for use in PTSD and neuropathic pain. Authors of this article published findings with NeuroDirectTM topical ketamine in treating PTSD and intractable depression in March 2023.[4] Ketamine is thought to produce strong analgesia in neuropathic pain states through inhibition of the NMDA receptor.[5,6]

The NMDA receptor has excitatory glutamic function at spinal and supraspinal sites involved in afferent transmission of nociceptive signals. In chronic pain states, prolonged nociceptive stimulation causes activation and up-regulation of NMDA receptors at dorsal horn synapses, resulting in increased and heightened pain signals to brain, so called "central sensitization." This is the major contributing factor in producing a chronic neuropathic pain state.

There is increasing evidence NMDA receptor antagonists, such as ketamine, attenuate excessive nociceptive input to brain, thereby providing an alternative means to treating chronic pain syndromes.[4] Other aspects of ketamine that may contribute to its analgesic effects include enhancement of descending inhibition and its anti-inflammatory effects.[7-9]

Antagonism of NMDA receptor by ketamine is thought responsible for its anesthetic and analgesic, as well as anti-depressive effects; the former, through prevention of "central sensitization." The antidepressant action involves norepi-

FIGURE 3

Neuropathic Pain Scale (NPS):

Quantifies severity of neuropathic pain

Mdcalc.com (Creator Dr. Bradley S. Galer)

Scores are based on patient response to questions about pain intensity. ***0 = no pain; 10 indicates most pain imaginable. Higher the score (maximum 100 points), the worse the neuropathic pain.***

Indication: Known neuropathy patient being followed and evaluated over time.

Pearls/Pitfalls : The NPS quantifies already diagnosed neuropathic pain and is NOT a diagnostic tool to determine if a patient's pain is neuropathic in origin.

Date: Time:
Before ketamine: After ketamine:
SCORING:
1. How intense is the pain?
2. How sharp is the pain?
3. How hot is the pain?
4. How dull is the pain?
5. How cold is the pain?
6. How sensitive is the skin to light touch?
7. How itchy is the pain?
8. How unpleasant is the pain?
9. If the pain is deep, how intense is the deep pain?
10. If the pain is on the surface, how intense is the surface pain?
TOTAL:

Additional questions : What is the time quality of the pain? Circle one:
1. Background pain present all the time, with occasional flare ups?
2. Single type of pain present all the time?
3. Single type of pain only sometimes present ?

nephrine, serotonin, and dopamine.

NMDA receptors exist on peripheral nerves and skin-free nerve-endings, allowing receptor antagonism to occur at these sites with topically applied drugs. Accordingly, ketamine applied to skin at specific anatomical areas can provide pain relief and also alleviate depression and anxiety.[10,11] Topically applied at the back of the neck at the hairline (BONATH), ketamine was found effective in treating PTSD and intractable depression.[4]

Persistent peripheral activation of NMDA receptors to spinal cord inter-neurons results in increased sensitivity to neural input, causing "central sensitization."[12-15] On the other hand, "peripheral sensitization" is acquired excitability of sensory nerves with decreased threshold to nociceptor activation.[16]

Accordingly, with location of NMDA receptors on both afferent somatic and visceral nerve axons, there is potential for treating various different pain conditions with ketamine.[17]

KETAMINE

Initially used as a general anesthetic, ketamine induces "dissociative anesthesia," a trance-like state providing pain relief, sedation, and amnesia. Short-term IV infusions of ketamine produce potent analgesia only during administration. Prolonged infusions (4-14 days) provide more long-term analgesic effects, up to months. Side effects of ketamine include psychedelic symptoms (hallucinations, memory defects, panic attacks), nausea/vomiting, somnolence, cardiovascular stimulation; and, hepatotoxicity.[18]

In controlled settings, ketamine is fairly well tolerated. Regardless, close monitoring of patients receiving systemic ketamine is mandatory; with particular attention to CNS and hemodynamic effects. Pending additional definitive proof, ketamine administration should be restricted to patients with intractable depression and therapy-resistant severe neuropathic pain.

Despite IV ketamine not formally approved for neuropathic pain or PTSD, ketamine infusion clinics have popped up at major cities throughout the United States. Without insurance coverage of infusions, therapy can be cost prohibitive, from $300-$2,000 per IV infusion, depending on dose and indication for treatment. Infusions last an hour or more, followed by an observation period for vital signs and side effects. Psychiatric side effects are frequent as well as elevated blood pressure and nausea.

Even at low sub-anesthetic intravenous doses, psychiatric side effects are prominent. A majority of patients report feeling "strange, spacey, woozy, or floating" or having visual distortions or numbness. Also frequently mentioned are speech difficulty, confusion, euphoria, drowsiness, and concentration problems. Psychotic symptoms such as "going into a hole, disappearing, feeling melting, experiencing colors, and hallucinations" are described by some 10% of people. Dizziness, blurred vision, dry mouth, hypertension, nausea, body temperature changes, or feeling flushed are common non-psychiatric side effects. Accordingly, a several-hour period of observation is recommended following IV ketamine infusion. Patients are not recommended to drive home afterward.

Ketamine has not been approved in the US for PTSD or depression or for use in neuropathic pain. However, an enantiomer of ketamine (esketamine, Spravato®) has been approved as a nasal spray for treatment-resistant depression in the United States and elsewhere. It is not, however, approved for treating neuropathic pain. Furthermore, there is an associated Risk Mitigation and Management Strategy (REMS) with its use, and the drug is made available only at designated treatment centers. The restricted program called SPRAVATO REMS exists because of the risks of serious adverse outcomes from sedation, dissociation, and abuse and misuse. It may only be dispensed and administered in certified healthcare settings by a healthcare provider, with monitoring for at least 2 hours following administration.[19]

UNIQUE NATURE OF TOPICAL NEURODIRECT™ KETAMINE

It is apparent ketamine can play an important role in treating intractable symptoms of neuropathic pain and PTSD. But limiting use is expense, inconvenience, potential side effects, and impracticality as maintenance therapy. We reported previously on the efficacy and convenience of at-home treatment NeuroDirect topical ketamine cream in alleviating persistent symptoms of PTSD and intractable depression.[4] We now report its efficacy in treating a wide variety of neuropathic pain conditions.

NeuroDirect (also known as Direct Effects™ technology) is a novel, patented delivery of neuro-affective compounds as cream applied to skin at the back of neck at the hairline, "BONATH." BONATH is a critical area of anatomy where access to afferent neural input to spinal cord and brain is achieved cutaneously through Trigeminal and Vagal Nerve Complexes at the upper cervical nerve roots, C1-C4. Free nerve-endings under skin surface are

Respiratory Drug Delivery Conferences

Delivering Pulmonary and Nasal Insights and Excellence for 35 Years

RDD®

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

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

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

Data from RDD 2022

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

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

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

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

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

activated by topically applied active drug, with neuro-chemical reactions occurring at specific receptors. Action potentials to the CNS as result of these chemical reactions provide therapeutic benefit. This occurs without requirement of drug entry into bloodstream, main source of side effects and drug interactions. Further, there are no restrictions placed by the blood-brain-barrier. The psychogenic effects encountered with intravenous, nasal spray, and other systemic ketamine uses are avoided. With NeuroDirect technology, benefits of psychedelic compounds may be achieved without concern for their potential systemic effects.[5]

Other neuro-affective compounds successfully used with NeuroDirect technology include: triptans, dopamine agonist apomorphine, tizanidine, phentermine, 4-amino pyridine; cannabinoids, in particular, CBD, CBG, and beta-caryophyllene; as well as opioids, amantadine, tramadol, and others. In these topical drug applications, therapeutic benefit was achieved within 10 minutes of application, as nerve impulses from skin free nerve-endings to brain travel at the same rate for all individuals. Without involvement of the bloodstream, usual systemic side effects associated with these compounds were not observed.

In summary, through mechanisms at NMDA receptors, various chemical and neuro-electrical processes responsible for symptoms related to neuropathic pain and PTSD may be addressed using a single compound, ketamine. Additionally, using ketamine with NeuroDirect technology allows potential undesirable side effects to be avoided, with therapeutic benefits achieved rapidly.

It is interesting to note both neuropathic pain syndromes and PTSD are abnormalities in brain pain processing with heightened perception and involvement of other physical and psychological functions.

NEURODIRECT™ KETAMINE CLINICAL DATA IN NEUROPATHIC PAIN

Single doses of NeuroDirect Ketamine 50 mg/ml were studied in 53 consecutive patents presenting to an out-patient General Neurology and Neuropsychiatry practice in Sarasota, FL, with various forms of neuropathic pain and Chronic Regional Pain Syndrome (CRPS). Patients were selected for in-office ketamine treatment based on their diagnoses and symptomatology. Outcome measures to evaluate the efficacy were:

- NUMERIC PAIN SCALE, 0-10, patient self-reported with 0 = no pain; 10 worst possible pain.
- NEUROPATHIC PAIN SCALE (NPS) (From 0-100. Each category is out of 10 with 10 being the worst pain category. This scale specifically aims to quantify

FIGURE 4

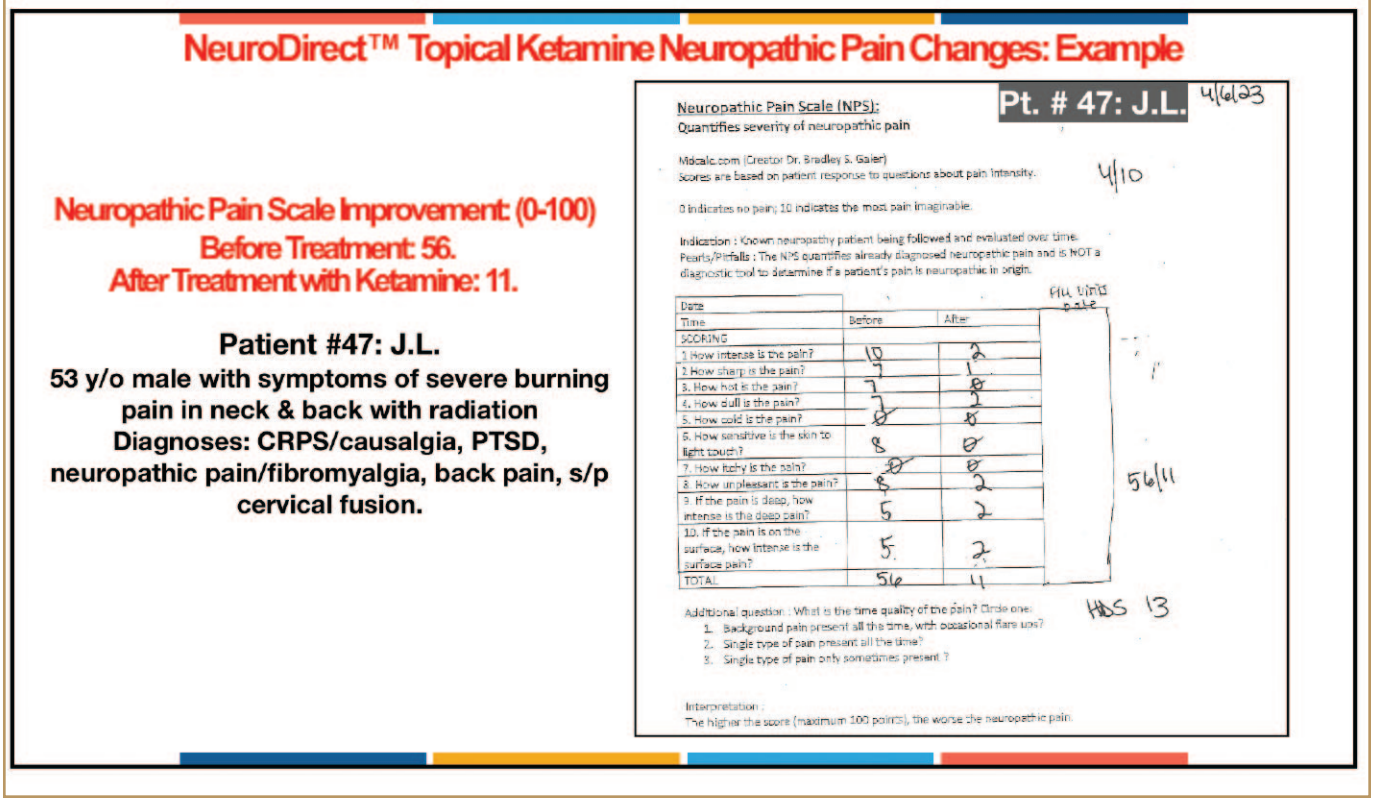


TABLE 1

NeuroDirect™ Ketamine in Neuropathic Pain: Leading Diagnoses Treated

53 patients: 35 females, 18 males
Age range: 19-84

-Back pain = 31 patients. Subdivided as follows:

Failed Back Surgery Syndrome = 5
Unspecified Chronic Lower Back Pain = 5
Lumbar laminectomy and fusion = 4
Thoracic pain = 4
Ankylosing Spondylitis = 3
Degenerative lumbar disc disease = 3
Lumbar radiculopathy = 3
Thoracic spondylosis = 2
Post lumbar synovial cyst resection = 1
Thoracic laminectomy and fusion = 1

***NOTE: MOST PATIENTS HAD MULTIPLE DIAGNOSES. THESE ARE THE NUMBER OF PATIENTS PER CONDITION*

-Neck pain = 20 patients. Subdivided as follows:
Cervical spondylosis = 8
Unspecified Neck Pain = 6
Cervical Fusion = 4
Cervical Stenosis = 2

-Fibromyalgia = 17 patients
-Arthralgia/arthritis = 16 patients
-Migraines/Headache disorder = 16 patients
-Neuropathic pain = 12 patients (I2 with diabetic peripheral neuropathy and 1 with central neuropathic pain syndrome)
-Anxiety / Depression = 12 patients
-Multiple Sclerosis = 5 patients
-Cognitive issues = 4 patients
-Trigeminal neuralgia = 3 patients
-CRPS (Chronic Regional Pain Syndrome) = 2 patients
-PTSD = 22 patients

features of neuropathic pain), Figure 3

- HAMILTON DEPRESSION RATING SCALE (Ham-D): multiple-item questionnaire providing indication of depression and treatment response. Self-assessed, with input of family member as corroboration. Designed to rate severity of depression, anxiety, and other symptoms associated with chronic pain syndromes and PTSD; evaluates mood, feelings of guilt, suicide ideation, insomnia, agitation, retardation, anxiety, weight loss, and other somatic symptoms.

TABLE 2

NeuroDirect™ Ketamine in Neuropathic Pain: Response to Ketamine

Response to Topical Ketamine cream application as reported by the patient:
Reduction in pain = 47 patients
Calm/ Relaxed sensation = 7 patients
Reduction in muscle stiffness / tension = 3 patients
Increased focus / alertness = 2 patients
Improved ROM >50% = 1 patient

Response to Ketamine Cream Application : Numerical measures:
PAIN SCALE (This is a scale from 0-10 where 0 indicates no pain; 5 moderate pain and 10 the worst pain possible)
2 patients showed a 7 point reduction in their pain 10-15 mins post ketamine application.
8 patients showed a 6 point reduction in their pain 10-15 mins post ketamine application.
Average of 3.4 point drop in the pain scale.

NEURODIRECT™ KETAMINE RESULTS

10-point Pain Scale:

- Pain reduction <10 minutes of application in >88 % patients.
- Average reduction in in all patients: 3.4/10. 7-point reduction in 2 patients; 6-point reduction in 8 patients.

Other areas of improvement after NeuroDirect ketamine:

- Reduction in muscle stiffness and tension: 3 patients
- >50% improved ROM: 1 patient
- More calm and relaxed: 7 patients
- Improved focus and alertness: 2 patients

Neuropathic Pain Scale, NPS (0 to 100 range):

- Average 21.6-point reduction in NPS following ketamine application
- 54-point reduction in NPS: 1 patient; 46-point reduction in 1; 45-point reduction in 2. (See Figure 5 on patient No. 47: J.L.)

Hamilton Depression Rating Scale, Ham-D (range 0-100):

- A baseline Ham-D on 35 patients: average score 27/100, demonstrating relationship between emotional and physical pain in chronic neuropathic pain states with need for a therapeutic intervention that targets both.

CONCLUSION & PREVALENCE OF NEUROPATHIC PAIN

NeuroDirect Ketamine, previously reported to benefit in management of PTSD is now found beneficial in neuropathic pain. Complex regional pain syndrome (CRPS), is an example of extreme unrelenting widespread form of neuropathic pain with associated vasomotor changes of affected limbs.(4,20) Targeting such chronic pain with a fast acting, non-systemic, convenient and easy to use at home NeuroDirect ketamine cream could be of significant benefit in patients with CRPS as well as other neuropathic pain states including chronic neck and back pain.

In 2021, approximately 20.9%, or 51.6 million, of adults in US experienced chronic pain; with 6.9% experiencing intense pain that limited their daily activities, according to CDC.[21,22]

Chronic pain, or pain that lasts at least 3 months, can be a debilitating condition that affects various aspects of life for many people. It has also been linked to substance use, depression, higher suicide risk and Alzheimer's disease. "Addressing chronic pain and improving the lives of persons living with pain is a public health imperative," wrote Rikard and colleagues.[22]

REFERENCES

1. Woolf CJ, American College of P, American Physiological S. Pain: moving from symptom control toward mechanism-specific pharmacologic management. Ann Intern Med. 2004;140(6):441-51.
2. Niesters M, Martini C, and Dahan A, Ketamine for chronic pain: risks and benefits, Br J Clin Pharmacol. 2014 Feb; 77(2): 357-367.
3. Maher D, Chen L, Mao J, Intravenous Ketamine Infusions for Neuropathic Pain Management: A Promising Therapy in Need of Optimization, Anesthesia & Analgesia 124(2):p 661-674, February 2017.
4. Aung-Din, R and Martin, C, NeuroDirect™ Ketamine: Novel, Non-Systemic Topical Therapy for PTSD & Associated Intractable Depression, Drug Development & Delivery. 2023;23(2):32-37.
5. Domino EF. Taming the ketamine tiger. Anesthesiology. 2010;113:876-886.
6. Petrenko AB, Yamakura T, Baba H, Shimoji K. The role of N-methyl-D-aspartate (NMDA) receptors in pain: a review. Anesth Analg. 2003;97:1108-1116.
7. Niesters M, Khalili-Mahani N, Martini C, Aarts L, van Gerven J, van Buchem MA, Dahan A, Rombouts S. Effect of subanesthetic ketamine on intrinsic functional brain connectivity: a placebo controlled functional magnetic resonance imaging study in healthy volunteers. Anesthesioloy. 2012;117:868-877. [PubMed] [Google Scholar].
8. Niesters M, Aarts L, Sarton E, Dahan A. Influence of ketamine and morphine on descending pain modulation in chronic pain patients: a randomized placebo controlled cross-over study. Br J Anaesth 2013. [Epub ahead of print] [PubMed].
9. Hirota K, Lambert DG. Ketamine: new uses for an old drug? Br J Anaesth. 2011;107:123-126. [PubMed] [Google Scholar].
10. Li N, Lee B, Liu RJ, Banasr M, Dwyer JM, Iwata M, Li XY, Aghajanian G, Duman RS. mTOR-dependent synapse formation underlies rapid antidepressant effects of NMDA antagonists. Science. 2010;329:959-964. [PMC free article] [PubMed] [Google Scholar].
11. Bowdle AT, Radant AD, Cowley DS, Kharash ED, Strassman RJ, Ray-Byrne PP. Psychedelic effects of ketamine in healthy volunteers. Anesthesiology. 1998;88:82-88. [PubMed] [Google Scholar].
12. McRoberts JA, Ennes HS, Marvizon JC, Fanselow MS, Mayer EA, Vissel B. Selective knockdown of NMDA receptors in primary afferent neurons decreases pain during phase 2 of the formalin test. Neuroscience. 2011;172:474-82. doi: 10.1016/j.neuroscience.2010.10.045. [PMC free article] [PubMed] [CrossRef] [Google Scholar].
13. Willert RP, Woolf CJ, Hobson AR, Delaney C, Thompson DG, Aziz Q. The development and maintenance of human visceral pain hypersensitivity is dependent on the N-methyl-D-aspartate receptor. Gastroenterology. 2004;126(3):683-92. [PubMed] [Google Scholar].
14. Petrenko AB, Yamakura T, Baba H, Shimoji K. The role of N-methyl-D-aspartate (NMDA) receptors in pain: a review. Anesth Analg. 2003;97(4):1108-16. [PubMed] [Google Scholar].
15. Parsons CG. NMDA receptors as targets for drug action in neuropathic pain. Eur J Pharmacol. 2001;429(1-3):71-8. [PubMed] [Google Scholar].
16. Bennett GJ. Update on the neurophysiology of pain transmission and modulation: focus on the NMDA-receptor. J Pain Symptom Manage. 2000;19(1 Suppl):S2-6. [PubMed] [Google Scholar].
17. Sigtermans MJ, van Hilten JJ, Bauer MCR, Arbous MS, Marinus J, Sarton EY, Dahan A. Ketamine produces effective and long-term pain relief in patients with Complex Regional Pain Syndrome Type 1. Pain. 2009;145:304-311. [PubMed] [Google Scholar].
18. Woolf TF, Adams JD. Biotransformation of ketamine, (Z)-6-hydroxyketamine, and (E)-6-hydroxyketamine by rat, rabbit, and human liver microsomal preparations. Xenobiotica. 1987;17:839-847.
19. Prescribing Information, including Boxed WARNINGS, and Medication Guide for SPRAVATO®, Janssen Pharmaceuticals, Inc. 2023.
20. Stanton-Hicks M. Complex regional pain syndrome: manifestations and the role of neurostimulation in its management. J Pain Symptom Manage. 2006 Apr;31(4 Suppl):S20-4. doi: 10.1016/j.jpainsymman.2005.12.011. PMID: 16647591.
21. Bascom E, 1 in 5 adults in US has chronic pain, healio.com/news, April 26, 2023.
22. Rikard SM, et al. MMWR Morb Mortal Wkly Rep. 2023;doi:10.15585/mmwr.mm7215a1.

BIOGRAPHIES

Dr. Ronald Aung-Din practices General Neurology & Neuro-Psychiatry in Sarasota, FL. He attended the University of Texas Southwestern Medical School, Dallas, TX, followed by residencies in Neurology and Neurosurgery at University of Florida. He has participated in over 60 pharmaceutical industry-sponsored clinical trials, functioning as Principal Investigator in drug research studies. He is also active in treating varied neurological and psychiatric conditions using delivery of CNS-active drugs with Neuro-Direct™ technology, for which 13 US and foreign patents have been granted to date. AfGin Pharma, LLC was founded in 2009 to advance the unique nature of this non-systemic drug delivery and its goal of *Enhanced Neuro-Therapeutics through Direct Effects Topical Technology*.

Dr. Chantelle G. Martin iwas born in Zimbabwe, Africa, and attended Medical School at the University of the Free State, Bloemfontein, South Africa, earning her Bachelor of Medicine and Bachelor of Surgery in 2016. She later completed 2 years of internship training at Grey's Hospital, Pietermaritzburg, South Africa; as well as a year of rural community service. She is currently in the midst of her Internal Medicine residency in the Atlanta, GA, area.

CLINICAL TRIALS

2023 & Beyond: How Technology is Changing the Face of Clinical Trials

By: Betsy Wagner and Marie E. Lamont

INTRODUCTION

The pandemic and ensuing changes to ways of working have exacerbated many challenges across different industries, especially healthcare settings and clinical research. Working through these challenges has also been a catalyst for change in how technology is used in these arenas. As we look ahead, industry leaders have a unique opportunity to leverage tech-enabled solutions that will drive advancement in developing new treatments. Across the industry, many stakeholders are not only receptive to the idea but are ready to move their sites and organizations forward in using these tools.

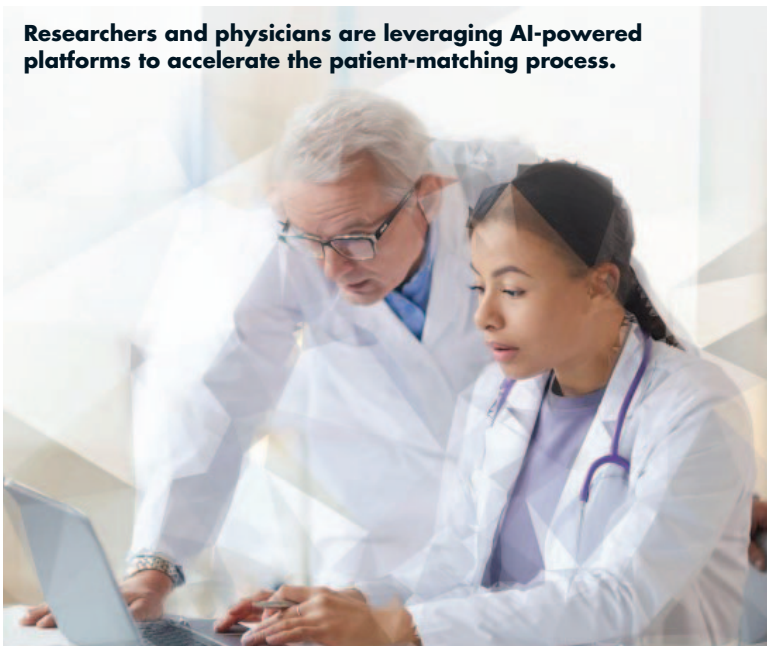
Before anyone can take full advantage of this opportunity, education about the technology and the practical benefits, viewed through the lens of understanding historical lessons learned, will be the critical next step.

THE CURRENT REALITY OF MATCHING CLINICAL TRIALS TO PATIENTS

When it comes to finding new treatments for patients facing life-threatening diseases or other illnesses, clinical trials can be the most powerful tool to offer. Yet, only a small percentage of eligible patients enroll in trials, with less than 5% of adult cancer patients selecting a clinical trial as a care option. While it may seem as though the patients are turning down these opportunities, many potential participants, including 55% of cancer patients, say they are willing to enroll in a trial if it's offered to them. This figure highlights that patients are not turning down offers for enrollment; rather, their clinicians are not armed with the resources to proactively match patients to trials and offer this opportunity. Due to this gap in recruitment for clinical trials, as many as 20% of cancer clinical trials tragically fail to start, and between 18%-40% never meet their accrual goals. At the same time, these situations mean patients are not being offered access to the most cutting-edge and foremost treatments on the horizon. Today, there are resources and solutions to do better by patients, treating healthcare providers, and sponsors developing new therapies.

Historically, the processes involved in clinical trial matching are extremely time-consuming and tedious, including screening for eligible patients to recruit by matching their health records to the stringent eligibility requirements of a trial. This work was done manually by staff hired at sites to review patients one by one, criterion by criterion. With the current staffing environment, many research sites are struggling to hire, train, and retain people for these roles. Without them, screening at a site slows to a crawl for most trials, harming the opportunity for patients as well as the operations of the site as a whole. Looking beyond resource constraints, this manual process also misses the opportunity to recruit a more diverse and representative population. For example, there continues to be a vast majority of White participants enrolling in

Researchers and physicians are leveraging AI-powered platforms to accelerate the patient-matching process.



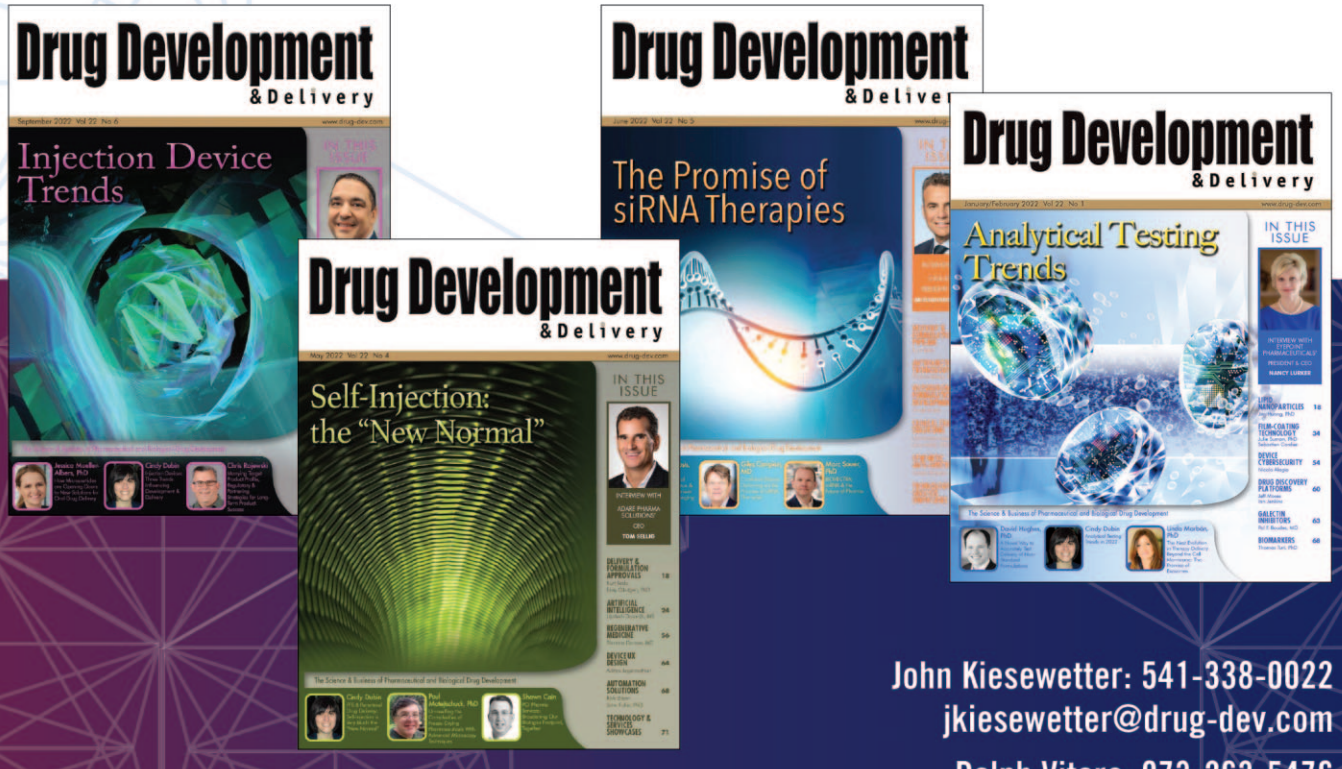
KEEPING YOU CONNECTED TO YOUR TARGET AUDIENCE.

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

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

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

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



John Kiesewetter: 541-338-0022
jkiesewetter@drug-dev.com
Ralph Vitaro: 973-263-5476
rvitaro@drug-dev.com
drug-dev.com

trials at an increased rate compared to other groups, such as Black/African American and Hispanic participants – who only make up about 13.6% and 18.9% of total trial enrollment. This representation is imperative for treatment efficacy and closing the heath gap for those who have not been accounted for in traditional trials.

Site workers are leveraging AI-enabled solutions to enhance the analysis of patient charts, and rapidly identify key data including biomarker information.

THE ROLE OF PRECISION MEDICINE IN CHOOSING TREATMENT OPTIONS

This process reflects an outdated model, especially in light of the growing trajectory toward precision medicine. As more treatments emerge that target specific biomarkers, patients have the advantage of receiving care that can be more effective and less toxic. Development of these drugs requires increasingly niche trials to ensure efficacy and safety, which start with identifying the patient population. While not every patient will be eligible for any given trial, new medical and technological advancements have opened the door to personalizing patient care, improving quality of life, and developing lifesaving treatments.

The most critical time to participate in research in a cancer patient's journey is upon referral, not when they have already run out of traditional treatment options. Unfortunately, this has been a misconception perpetuated by a lack of available information and resources. In a study by Penn State, between 2004 and 2015, only 0.1% of the more than 12 million newly diagnosed cancer patients were enrolled in clinical trials as their first treatment option.

As healthcare and life sciences have advanced, there has been immense growth in precision medicine and next-generation gene sequencing in recent years. Instead of treating all patients with the same sequence of options, it's now possible to determine the genetic information of the patients' specific disease and match them to molecularly compatible treatments, often still in trial stages. The sooner physicians and researchers are able to identify the genetic makeup of each patient's disease, the higher the probability of slowing or stopping its growth. Additionally, using targeted therapy prevents the toxicity and growth of resistance that can render treatments dangerous to patients.

To help power the discovery of these biomarker-driven therapies, the maturation of artificial intelligence (AI) technology is revealing a new realm of possibilities that will make implementation and collaboration for the next generation of clinical trials a reality.

HOW TECHNOLOGY WILL HELP OVERCOME BARRIERS

When it comes to enabling clinical trial matching, the most helpful resource available is AI-powered platforms. Patented technology exists today that allows researchers and physicians to easily navigate patient data and optimize their resources by both finding the precise pool of candidates that meet the requirements for their trials and by choosing the right trials to open for the patient population they treat.

The research team searching for patients for their trial portfolio, as previously noted, had been manually reviewing every patient's records to identify those who could be eligible to participate in a trial. Given the rise of precision trials, they are increasingly looking for the biomarkers that drive treatment options. What if, instead of reviewing chart after chart, they received a summary of patients with that biomarker from a tech platform that used AI to match those patients to those criteria? This team can now focus the hours they were spending on screening, instead, on patient care, study coordination, or data collection. With the numerous duties assigned to most research staff, this efficiency saves the site time and resources and ensures they don't miss any potential patients.

These technology solutions also allow for better trial and site selection, which can make patient matching easier and more efficient to the benefit of the entire trial lifecycle. By identifying the potential patient

population at a site using AI, instead of the traditional methods of "best guess" and historical enrollment in past trials, sites can make a compelling case to sponsors for their inclusion in a trial. Sponsors can ensure their sites will successfully enroll, avoiding the waste of finding replacements for underperforming sites and even the failure of entire trials. By facilitating these strong-enrolling sites, which is increasingly difficult for rare populations, the relationship between sites and sponsors can be one of trust and partnership, which will build more opportunities for patients across all sites.

AI-enabled patient matching also allows further nuance in several areas of clinical research. These tools can facilitate trials to overcome the barriers of implicit bias, bringing greater potential to enrollment of diverse patients. Creating objective queries will allow the data to speak for itself, without a lens of prejudice or presumption that can serve as an unconscious barrier for investigators to enrolling willing participants. With the FDA's new requirements for trials to identify and target racial/ethnic and other minority groups for enrollment, this opportunity will serve all players in the arena, especially historically overlooked patients. Beyond patient identification, AI has been applied to health records to pull clinical trial data directly out of site records and into data capture systems. While this technique is still emerging and has much to grapple with before becoming standard practice, the potential efficiencies for sites and sponsors is enormous. However, many challenges remain to the application of AI on clinical research. Data variability is significant and will drive the development of new AI breakthroughs, which will then present new opportunities in an ever-evolving dynamic.

While implementation of new AI-powered technology will require upfront costs and effort, the long-term payoff will be far more valuable than continuing to use traditional tools and methods. Physicians can offer their patients state-of-the-art treatments as their first line of defense; researchers can make ground-breaking discoveries that are representative of a diverse patient population; and clinics, both academic- and community-based, will be able to improve both their bottom line and sponsor relationships by successfully recruiting and retaining clinical trial participants.

MOVING HEALTHCARE FORWARD BY ACCELERATING THE PATIENT ENROLLMENT JOURNEY

We are on the cusp of a complete reimagining of how cancer research is done, all with the goal of giving patients hope for a better future even after a cancer diagnosis. Best of all, advanced technology is readily available today and has been deployed with success in driving efficiencies that can be implemented on a broad scale. The next step to moving healthcare forward is to provide the education and support needed to assist healthcare organizations to make the transition as seamless as possible and ensure they can tap into all the capabilities intuitive and intelligent technology can offer.◆

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

BIOGRAPHIES

Betsy Wagner is a seasoned clinical research professional with 15+ years of progressive site, CRO, and vendor experience. She has a deep background in clinical trial operations and patient recruitment, using traditional and tech-enabled solutions. She has overseen departmental growth in both academic and community research settings, providing a variety of experiences to inform how sites can excel in order to facilitate more patients having access to more trials.

Marie E. Lamont is the Global Head of Real Word Evidence Data Strategy, Access, and Enablement at IQVIA and the General Manager at Inteliquet, a patient-matching clinical trial software company. She is the former President of the Patient Services Business at Dohmen Life Science Services (DLSS), which was sold and is now part of EVERSANA. Prior to DLSS, she was Global Head of Business Strategy and Commercial Operations for Rare disease at Sanofi Genzyme. She had stewardship for the $2.9 billion business. She can be reached at marie.lamont@iqvia.com.

NATURAL LANGUAGE PROCESSING

Mandatory IDMP Compliance is Almost Here – How NLP Can Help

By: Simon Johns

INTRODUCTION

The Identification of Medicinal Products (IDMP) is a set of five standards developed by the International Organization for Standardization (ISO) to help streamline and improve the safety of pharmaceutical operations across the entire drug development cycle. The overarching goal is to enhance patient safety through an improvement in the consistency, accuracy, and speed of sharing adverse events (AE) and safety signal reporting. These standards were originally developed in 2012 and have been periodically updated since. Now, 11 years following development, the IDMP standards are set to become mandatory this year.

THE IDMP FRAMEWORK

The five standards that define the IDMP framework are described in Table 1. IDMP specifies the use of standardized definitions across global regulatory and health authorities for the descriptions and identification of medicinal products, with the purpose of facilitating reliable and consistent exchange of medicinal product information. IDMP impacts many aspects of the drug lifecycle, including marketing, data management, regulatory operations and affairs, and pharmacovigilance. The five standards that make up IDMP look to homogenize the descriptions of marketed medicinal products around the world, with the main end goal being improved patient safety. These standards have been found to be impactful in practice; the EU commission estimates that improved pharmacovigilance regulations will save up to 5,910 lives per year.

TIMELINE

The timeline for implementation differs by health authority. The European Medicines Agency (EMA) is set to be the first health authority to mandate IDMP compliance in 2023 and recently released its guidelines for implementation. Other global health authorities across the world will soon implement IDMP, and the FDA is one of the next in line. While these standards will have a large, positive impact in the space, pharma organizations need to prepare for the challenges that come with the transition.

DATA CONSIDERATIONS FOR IDMP

Medicine safety is a global issue; there is an urgent need for accurate medicinal data, but this key data does not always transfer well. With IDMP, consistent data for drug processes will strengthen drug safety and regulations across borders. It will also be extremely beneficial in times of medicine shortages – the harmonization of drug descriptions can assist in finding a different, suitable drug option quickly.

IDMP compliance will take resources, time, and investment. IDMP-related data is captured in unstructured data containers, and these documents may have different formats, different languages, or different phrasing used for the same terminology. Different authors tend to have individualized styles, and these factors create difficulties in manual search when capturing data entries from both internal and external document sources for IDMP. Keyword searches and manual curation are not only slow, but they are tedious, limited, and prone to errors. The capture of 300-

TABLE 1

Framework	Description
ISO 11615 – Medicinal Product Information (MPI)	This standard is used to describe the detailed data elements and their structural relationships for regulated medicinal product unique identification. This entails the product name, packaging, manufacturer, marketing authorization, clinical particulars and more.
ISO 11616 – Pharmaceutical Product Information (PPI)	This standard associates medicinal products with similar or the same composition based on reference strength, dosage form and substance strength.
ISO 11238 – Substances Identification (SI)	This standard defines substances in a medicinal product by their general characteristics.
ISO 11239 – Dosage Form and Route Administration	This standard looks at dosage forms, routes of administration, units of presentation, and packaging.
ISO 11240 – Units of Measurements (UoM)	This standard specifies the rules for the usage of UoM for traceability, as well as specifies the requirement of UoM in coded form and mapping between different languages and terminology.

2000 data entities per product demands major investment.

AI & NLP FOR IDMP COMPLIANCE

This is where Natural language processing (NLP) emerges as an asset. NLP is a form of artificial intelligence (AI) that has the ability to understand human language, both written and spoken. NLP can scan through documents or data to process and organize the content. NLP reduces time, effort, and the overuse of resources that emerge with extracting, structuring, and standardizing required data elements from unstructured IDMP text documents.

Around 80% of biomedical data is locked in unstructured text – without access to all text, information and insights are missed and lost. NLP transforms text into structured information and metadata – not only replacing the need for manual keyword search and cutting down on the time required, but divulging more information as well. In relation to IDMP, the documents and rich text data would be in the form of eCTD documents, regulatory models, field notes, or even social media posts. NLP can sift through documents and find different words, expressions, or grammar with the same meaning, or the same word with a different context. The information of the specific query posed is then highlighted and surfaced in a structured format. This reduces the efforts needed to abide by the IDMP standards and assists in a smooth transition to the new requirements.

IDMP PREPARATION TAKEAWAYS

The best way to prepare for IDMP implementation is by knowing exactly what is required to achieve such implementation and how to get there. With the US scheduled to implement IDMP this year and the EU in the process of implementation, IDMP is no longer just a distant requirement. It is happening now, and all organizations should be prepared for mandatory use this year. ◆

BIOGRAPHY

Simon Johns has more than 25 years of experience supporting customer projects across all stages of drug development and the full product lifecycle. As Director of Medical Information (MI) and Marketed Product Safety at IQVIA, he has been managing global MI projects focused on process optimization and technology enablement that drive enhanced efficiency and customer engagement. He is a member of the European DIA Medical Information and Communications Training Team, advising pharmaceutical companies on best industry practices, innovation, and automation. He speaks regularly on topics ranging from implementing suitable technologies and innovations to optimize MI to the benefits of integrating MI and pharmacovigilance to increase compliance and product value, leveraging IQVIA's Local Affiliate Product Services (LAPS), which provide full support for MI and local country pharmacovigilance requirements.

Hybrid Supplier

Actylis is a leading global manufacturer of critical raw materials and performance ingredients serving the Life Sciences industry. Through our hybrid approach we provide combined capabilities in GMP manufacturing and global sourcing of raw materials and ingredients, offering flexibility and unrivaled choice to pharmaceutical and biopharmaceutical companies.Thanks to our hybrid manufacturing / sourcing model we can supply solutions for over 3,000 compounds, including excipients, cell culture ingredients, buffers, process solutions, PIs, APIs, Water for Injection, amino acids, nucleosides and nucleotides. We also offer GMP custom manufacturing, ingredient development, custom packaging, R&D and analytical services. All our products are backed by world-class quality, reliable delivery, and a strong regulatory record. Discover Actylis and explore our raw materials and ingredients portfolio. For more information, visit Actylis at **www.actylis.com.**

Specialty CDMO

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

CDMO Services

Ajinomoto Bio-Pharma Services is a fully integrated contract development and manufacturing organization, with sites in Belgium, United States, Japan, and India, providing comprehensive process development services, cGMP manufacturing and drug product fill finish services of small molecule and large molecule APIs and intermediates. Ajinomoto Bio-Pharma Services offers a broad range of innovative platforms and capabilities to rapidly scale from clinical and pilot programs to commercial quantities, including: Corynex technologies, oligonucleotide synthesis, high potency APIs (HPAPI), biocatalysis, continuous flow manufacturing, and more. Ajinomoto Bio-Pharma Services is dedicated to providing a high level of quality and service to meet our clients' needs. For more information, contact Ajinomoto Bio-Pharma Services at **www.AjiBio-Pharma.com**.

CDMO Services

Alcami is a contract development, manufacturing, and testing organization headquartered in North Carolina with over 40 years of experience advancing products through every stage of the development lifecycle. Approximately 700 Alcami employees across four campuses in the United States serve biologics and pharmaceutical companies of all sizes, helping to deliver breakthrough therapies to patients faster. Alcami provides customizable and innovative solutions for formulation development, analytical development and testing services, clinical and commercial finished dosage form manufacturing (oral solid dose and parenteral), packaging, and stability services. For more information, visit Alcami at **www.alcaminow.com**.

Microcrystalline Cellulose

Asahi Kasei microcrystalline cellulose (MCC) Ceolus™ brings a key difference compared to standard MCC products: its high performance stemming from innovative particle morphology. It enables challenging formulations with poorly compactible APIs or high-dose APIs. It solves tableting issues, such as capping or sticking. It also enables unique and patient-friendly dosage forms, including MUPS and small tablets. In addition, less black particles, less impurities, including nitrite and nitrate, which may cause nitrosamine-associated risk, and the consistent high quality of Ceolus™ directly contributes to the quality improvement of customers' formulations. For more information, visit Asahi Kasei at **www.ceolus.com/en/.**

Formulation Development

Ascendia Pharmaceuticals is a speciality CDMO dedicated to developing enhanced formulations of existing drug products, and enabling formulations for pre-clinical and clinical-stage drug candidates. We specialize in developing formulation solutions for poorly water-soluble molecules and other challenging development projects. Combining our extensive knowledge and experience of formulation capabilities with our suite of nano-particle technologies, we can assess the feasibility of a broad array of robust formulation options to improve a drug's bioavailability. Thusly decreasing the amount of drug and the number of injections and greatly reducing in some cases the daily pill-burden from 20 to 4. Ascendia's expertise spans across (IV, SC, or IM), injection, ophthalmic, transdermal, nasal delivery, along with immediate- and controlled-release products for oral administration and complex generics. For more information, visit Ascendia at **www.ascendiapharma.com.**

Global CDMO

BIOVECTRA is a full-service CDMO specializing in the clinical-to-commercial-scale production of high-quality regulated APIs and intermediates, including biologics, synthetic small molecules, pDNA and mRNA, highly potent APIs, and bioreagents. Our teams leverage decades of expertise and a proven track record of excellence to optimize, adapt, and perfect innovative technologies and drug substance development approaches to deliver world-class solutions for pharmaceutical manufacturing. We offer: over 50 years of pharmaceutical manufacturing experience, flexible, creative systems designed to deliver solutions quickly and efficiently, and extensive regulatory expertise backed by long-standing relationships with major regulatory bodies For more information, visit BIOVECTRA at **www.BIOVECTRA.com.**

International CGMP CDMO

Bora Pharmaceuticals is a premier international CGMP CDMO specializing in complex oral solid dosage (tablet & capsules), liquids (solutions, suspensions, & nasal sprays) and semi-solids (creams & gels) pharmaceutical Rx and OTC products for late-phase Clinical through Commercial manufacturing and packaging. Bora owns and operates three state-of-the-art CGMP manufacturing facilities (Taiwan and Canada) built to the highest international standards for manufacturing, packaging, R&D, and analytical testing. For more information, visit Bora Pharmaceuticals at **https://www.boracorpcdmo.com/.**

Platform Technology

Captisol is a patent-protected, chemically modified cyclodextrin with a structure designed to optimize the solubility and stability of drugs. Captisol was invented and initially developed by scientists in the laboratories of Dr. Valentino Stella at the University of Kansas' Higuchi Biosciences Center for specific use in drug development and formulation. This unique technology has enabled 11 FDA-approved products, including Onyx Pharmaceuticals' Kyprolis®, Baxter International's Nexterone®, and Merck's NOXAFIL IV. There are more than 30 Captisol-enabled products currently in clinical development. For more information, visit Captisol at **www.captisol.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.**

Differentiated Injectable Delivery

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

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**.

ENVISION YOUR IMPACT

Honeywell

Aclar® film delivers a crystal-clear, high moisture barrier to protect medicines, while significantly reducing pack size, waste, and carbon emissions, when compared to the same product packaged in Cold Form Foil (CFF). Try the Aclar® Impact Estimator tool today! Gain data-driven insight to see what you can achieve by using Aclar®, including: the number of shipping containers of packaging material that can be saved annually, the reduction in transportation-related CO_2 emissions, and a unique view regarding waste reduction. For more information, visit **Honeywell at https://hwll.co/8leoao.**

Injectable Drug Delivery

Owen Mumford
Pharmaceutical Services

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

Global CDMO

pci
PHARMA SERVICES

PCI is a leading global CDMO, providing integrated end-to-end drug development, manufacturing and packaging solutions to increase product speed to market and opportunities for commercial success. PCI brings the proven experience that comes with more than 90 successful product launches each year and over 5 decades in the healthcare services business. We currently have 30 sites across Australia, Canada, US, UK, and Europe, with over 4,300 employees that work to bring life-changing therapies to patients. Leading technology and continued investment enable us to address global drug development needs throughout the product lifecycle, collaborating with our clients to improve patients' lives. For more information, visit PCI at **www.pci.com.**

Specialized Products & Services

Pfanstiehl
Delivering on The Promise of Purity

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.**

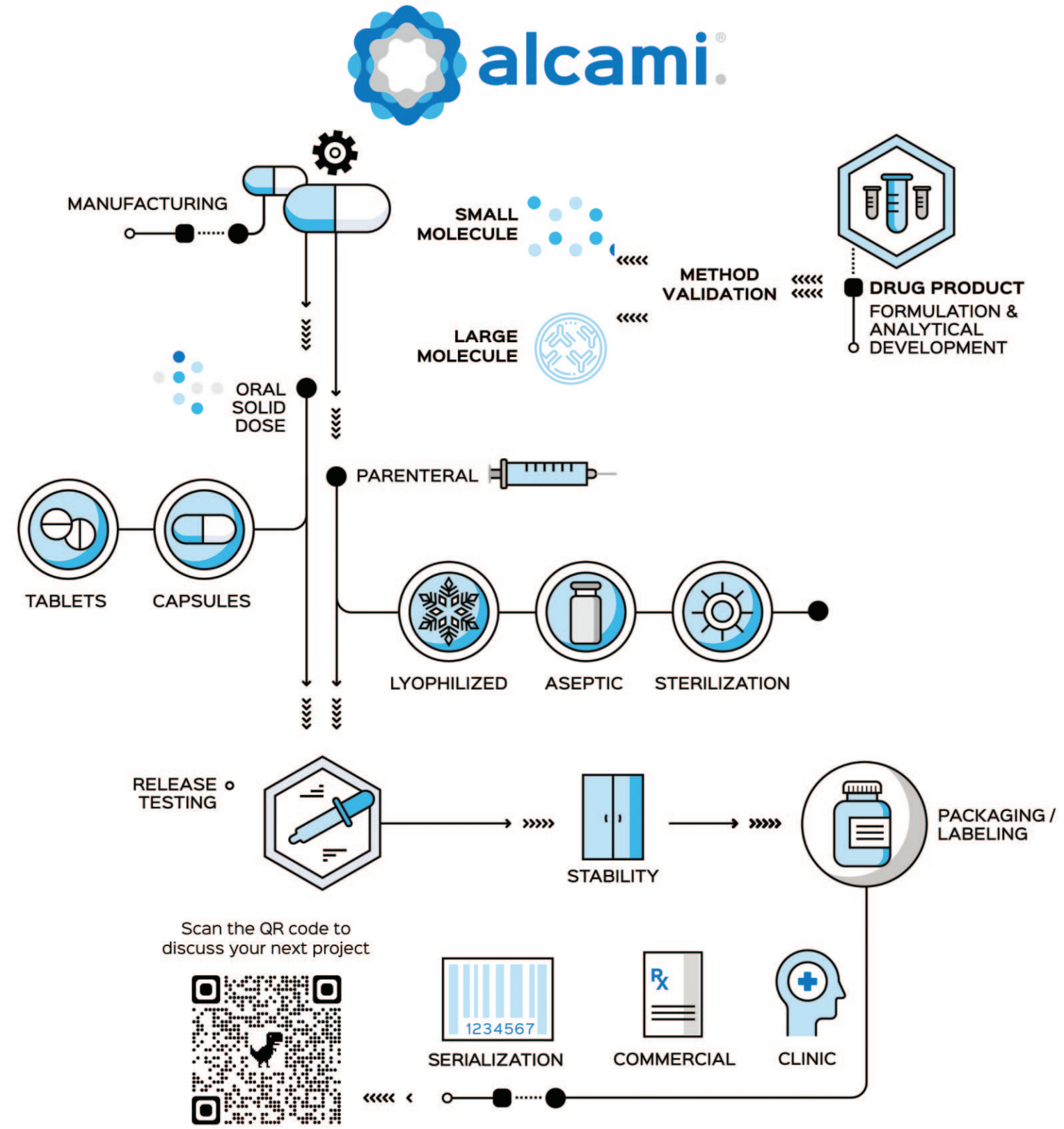
Specialized CDMO

SEVER
PHARMA SOLUTIONS

Sever Pharma Solutions, a CDMO providing customers with unique capabilities and expertise, brings your pharmaceutical ideas to life by offering expertise in Polymer- based dosage forms, including highly potent drug dosage development. We enhance your reach by ensuring your products benefit patients all over the world. We increase your efficiency by providing you with a complete value chain to offer you an optimized end-to-end solution. We improve your product and outcome by adding value through all development and manufacturing processes. We are Extrusion. We are Polymer-Based Dosage Forms. We are Formulation of Highly Potent dosage forms. We are Long-Acting Implants. We are Solid Dosage Forms. We are Injection Molding. We are Aseptic Fill and Finish. For more information, visit Sever Pharma Solutions at **www.severpharmasolutions.com.**

October 2023 Advertiser Index

COMPANY	PAGE	CONTACT	WEBSITE
Adare Pharma Services	7	BusDev@adareps.com	adarepharmasolutions.com
Alcami	76		alcaminow.com
Asahi Kasei	19	eolus_2@om.asahi-kasei.co.jp	www.ceolus.com/en/
Ascendia Pharma	9	bd@ascendiapharma.com	www.ascendiapharma.com
Drug Development & Delivery	4,57	(973) 263-5476	www.drug-dev.com
Ligand (Captisol)	13	cdinfo@captisol.com	www.captisol.com
Celanese	27	healthcare@celanese.com	www.vitaldose.com
Credence Medsystems	2	info@CredenceMed.com	www.CredenceMed.com
Gattefosse	3	infopharma@gattefosse.com	www.gattefosse.com
Honeywell (Aclar)	15		https://advancedmaterials.honeywell.com/us/en/initiative/aclar-calculator?
Nicklaus Marketing	42	(973) 5380450	www.nicklausmarketing.com
Owen Mumford	5	pharmaservices@owenmumford.com	www.ompharmaservices.com
PCI Pharma Services	17	(215) 613-3600	www.pci.com
Pfanstiehl	11	s@pfanstiehl.com	www.pfanstiehl.com
PharmaCircle	30,31	(800) 439-5130	www.pharmacircle.com
RDD	62	info@rddonline.com	Rddonline.com
Sever Pharma Solutions	35		Severpharmasolutions.com



Solutions, Delivered.

alcaminow.com |