Drug Development & Delivery

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Engineering Extracellular Vesicles

The Science & Business of Pharmaceutical and Biological Drug Development

Jeremy Graff, PhD
The Evolution of Cancer Vaccines: Moving Beyond Failure & a New Era for Cancer Treatment

David Lowe, PhD
Engineering Extracellular Vesicles to Create Next-Generation Therapeutics

Steven Kaufman
Owen Mumford & Stevanato Group: Collaborating to Produce Aidaptus® Auto-injector

IN THIS ISSUE

INTERVIEW WITH

CREDENCE MEDSYSTEMS'

CHIEF OPERATING OFFICER

JEFFREY TILLACK

GATTEFOSSÉ

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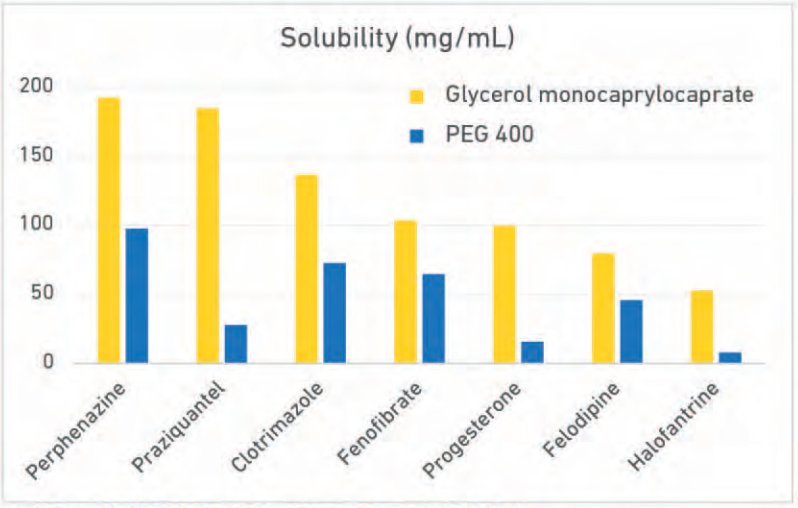

Alskar L.C. (2016) Mol. Pharmaceutics 13. 251-261

Key Features:

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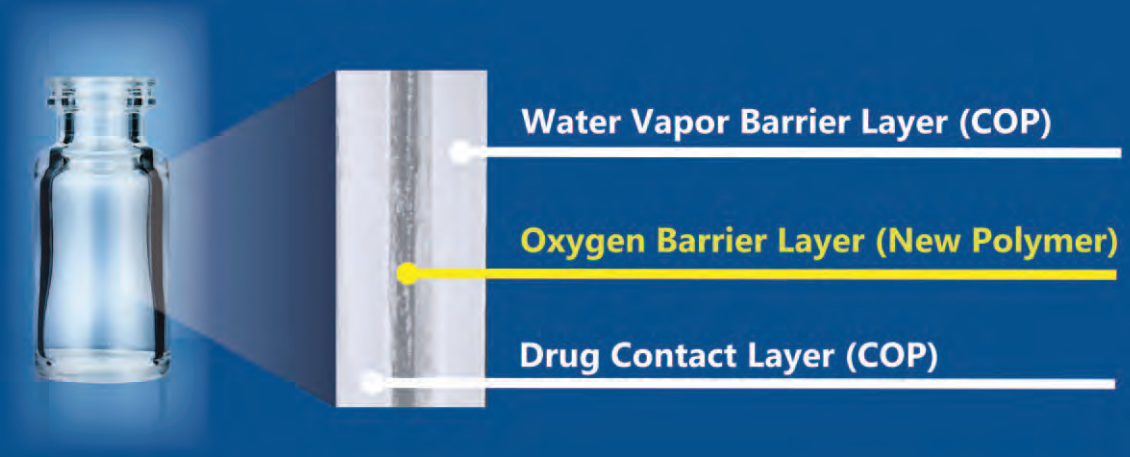

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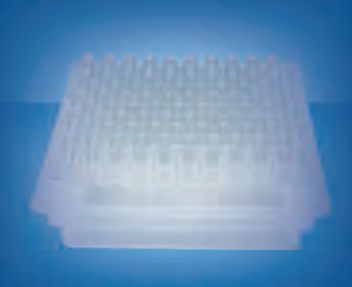

Nest & Tub for Vial

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1942-2022 INTO THE FUTURE... WITH CONFIDENCE AND CONSCIENCE

Engineering Extracellular Vesicles

"EVs exhibit key properties that make them extremely attractive as therapeutics, particularly their safety profile and potential for low immunogenicity. In order to effectively unlock this potential, some key challenges remain, such as the development of EV product manufacture and characterization methodologies and rapid pharmacokinetics."

p.33

Table of Contents

CAN YOUR CDMO TRANSFORM A DRUG FORMULATION MADE FOR HER

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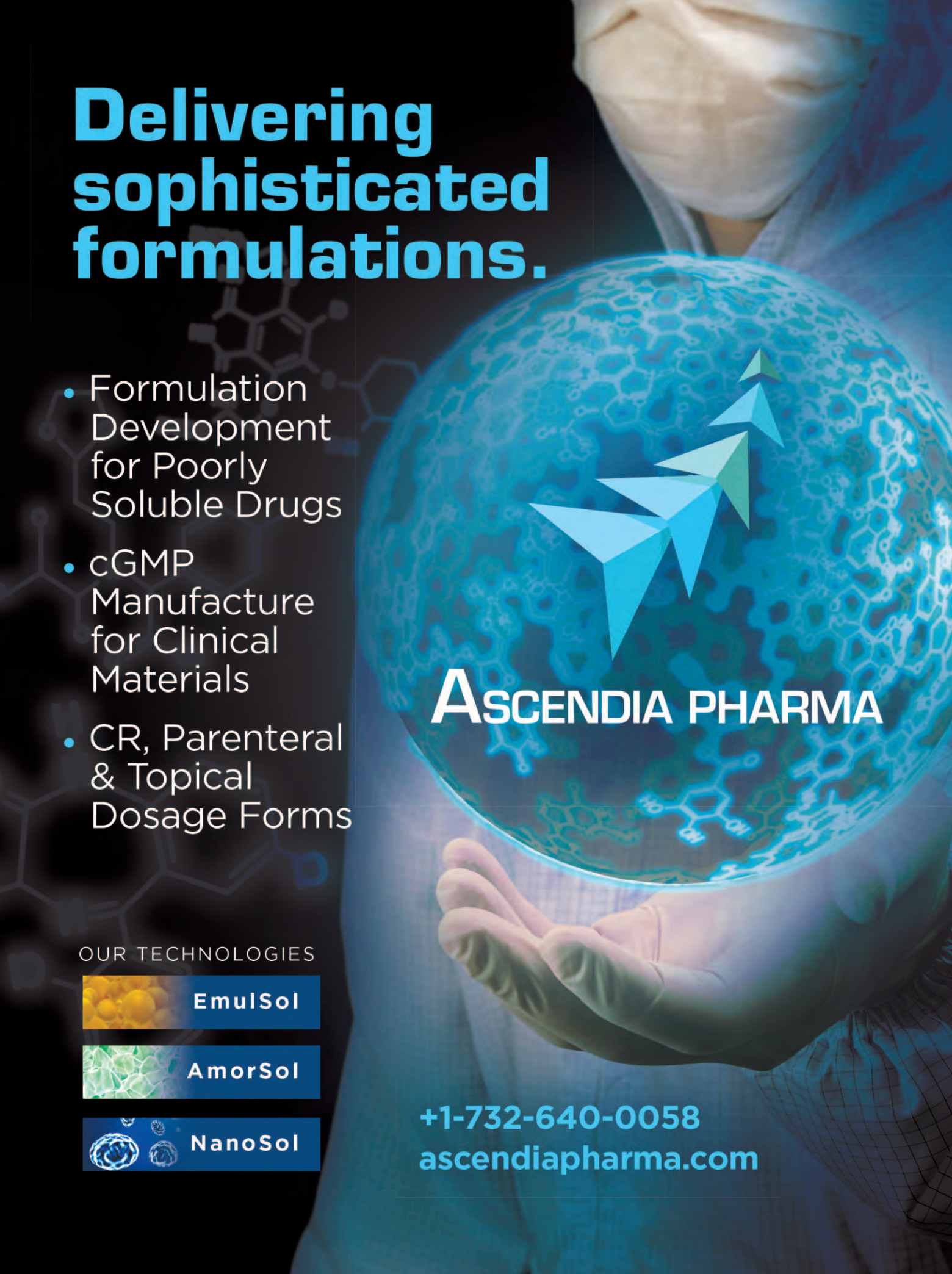
p.55

Table of Contents

Departments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ProtaGene Names Pharmaceutical Industry Leader Raymond Kaiser as CEO to Drive Next Stages of Growth

ProtaGene GmbH recently announced the appointment of Raymond Kaiser, PhD, as Chief Executive Officer. Ray will drive the continued innovation and growth strategy for the company's advanced analytical services.

Ray first joined ProtaGene earlier this year as Chief Operating Officer. He brings over 26 years of experience in the biopharmaceutical and CRO industries, including research and development, quality assurance/quality control, technical support of biopharmaceutical products, protein characterization, and application of Six Sigma methodologies.

Former CEO Martin Blüggel, who remains engaged on the Board of Directors, founded Protagen in 1997 and successfully navigated the merger of four organizations, each driven by scientific analytical excellence and market leadership in biologic and cell and gene therapy development, to form the advanced analytical leader, ProtaGene. With the recently completed merger with GeneWerk and partnership with healthcare growth investor Ampersand Capital Partners, ProtaGene will continue building its team and capabilities to support today's increasingly complex therapeutic development programs.

"ProtaGene is incredibly well-positioned to serve as an analytical leader that supports the development of diverse therapeutic modalities," said Blüggel. "It has been an extraordinary experience building the company, and now on the 25th anniversary, I entrust Ray, an experienced executive, to lead ProtaGene to future success. With growing operations in North America and Europe, the company under Ray's leadership is well prepared to serve our international sponsors within the biologics and cell and gene therapy sectors."

"With our strong market positioning in North America and Europe, combined platforms in advanced biologic and cell and gene therapy analytical development, and focus on quality systems and strategic project management, I see no limits to what ProtaGene can accomplish," added Dr. Kaiser. "As an increasing number of novel therapeutics enter the development pipeline, ProtaGene is prepared to rise to the challenges of these new products and modalities. Ultimately, I am thrilled and privileged to lead ProtaGene as the analytic partner of choice to deliver therapeutics to patients in need quickly."

Before joining ProtaGene, Ray was the Chief Operating Officer at Nexelis, overseeing operations, business strategy, and enhanced service offerings for pre-clinical and clinical bioanalytical testing. He earned his PhD in Analytical Chemistry from Purdue University and his Master of Science in Organic Chemistry from St. Louis University. Dr. Kaiser has published over 50 papers and patents on biologics and vaccine development, manufacturing, and characterization.

ProtaGene is a world-leading CRO partner for the biopharmaceutical and cell and gene therapy industries. From discovery to product commercialization, ProtaGene provides the most advanced, integrated, and complete protein and gene analytic capabilities and packages. A unique combination of protein- and gene-based analytical platforms make ProtaGene the leading analytic service provider in biologics and cell and gene therapy development. The organization operates four sites in Europe and North America and works in advanced therapeutic platforms with leading biopharmaceutical and gene therapy companies worldwide.

Evoke Pharma Receives Notice of Allowance From USPTO for a Patent Related to GIMOTI

Evoke Pharma, Inc. recently announced the USPTO issued a Notice of Allowance for US Application No. 16/469,092 for GIMOTI. When granted, the patent will cover methods for treating moderate-to-severe gastroparesis with metoclopramide with an intranasal route of administration. Once issued, the patent, titled Treatment of Moderate and Severe Gastroparesis, will expire in 2037. The patent will add to Evoke's existing US FDA Orange Book-listed patents and other patents in the EU, Japan, and Mexico.

GIMOTI is the first and only FDA-approved novel nasal formulation of metoclopramide that is commercially available and specifically designed to deliver a non-oral dose of metoclopramide for the relief of symptoms in adults with acute and recurrent diabetic gastroparesis. Non-oral delivery is an important treatment option as gastroparesis causes oral medications to be unpredictably absorbed and vulnerable to one of the key symptoms of the disease, vomiting.

"The patent protects our Phase 3 clinical trial outcomes and data showing efficacy with nasal metoclopramide formulations for persons suffering from moderate-to-severe diabetic gastroparesis. The grant of this new patent further enhances Evoke's growing position in this market and our continued efforts to ensure patients and doctors have access to GIMOTI in the US," said Matt D'Onofrio, Chief Business Officer of Evoke Pharma. "Through market surveys and healthcare provider and patient anecdotes, we've learned that there is an imperative need for a nasal formulation of metoclopramide rather than the traditional standard of care. Therefore, we believe the transition from oral administration of metoclopramide to a nasal route is revolutionary for both patients and doctors, and we are thrilled to have IP protections in place to protect a novel product like GIMOTI."

Evoke is a specialty pharmaceutical company focused primarily on the development of drugs to treat GI disorders and diseases. The company developed, commercialized and markets GIMOTI, a nasal spray formulation of metoclopramide, for the relief of symptoms associated with acute and recurrent diabetic gastroparesis in adults. Diabetic gastroparesis is a GI disorder affecting millions of patients worldwide, in which the stomach takes too long to empty its contents resulting in serious GI symptoms as well as other systemic complications. The gastric delay caused by gastroparesis can compromise absorption of orally administered medications. Prior to FDA approval to commercially market GIMOTI, metoclopramide was only available in oral and injectable formulations and remains the only drug currently approved in the US to treat gastroparesis. For more information, visit www.EvokePharma.com.

Wheeler Bio Announces President & Chief Operating Officer

Wheeler Bio, a new contract development and manufacturing organization (CDMO) specializing in the cell line development, process development, and small batch clinical production of antibodies, has announced the appointment of Dr. Roger Lias as President and Chief Operating Officer.

Roger most recently served as Chief Commercial Officer at Vibalogics, a viral vector CDMO that was acquired this year by Recipharm. In his capacity, Roger not only helped position Vibalogics for M&A success, but was also integral in a major capital expansion project in the US. Roger brings a wealth of experience in the biologics CDMO arena, having held senior commercial roles at Lonza and Diosynth before becoming a member of the founding management teams at KBI Biopharma, Cytovance Biologics, and Eden Biodesign. More recently, Roger was the Chief Executive Officer at Avid Bioservices and Stelis Biopharma. At both companies, he was responsible for the successful transition to dedicated CDMO models.

"Roger has been building, operating, and growing CDMOs for nearly 25 years. His depth of industry knowledge, relationships, and financing experience will help propel Wheeler's transition into the GMP arena in 2023 and beyond," said Dr. Jesse McCool, Wheeler's CEO. "I am thrilled that Roger has joined my team. He will be a tremendous asset to our customers and shareholders."

Wheeler Bio brings biologics drug innovators, discovery CROs, and CDMOs together to solve an outdated industry bottleneck with a unique partnering model, built on shared success and lasting collaborations. The typical momentum drop between discovery and development poses significant challenges for emerging biopharma companies adding technical, financial, and regulatory risks. Wheeler believes these lifecycle challenges can be reduced with more democratization of manufacturing platforms.

"I'm delighted to be joining the co-founders Jesse McCool, Christian Kanady (Echo), and Errik Anderson (Alloy Therapeutics) along with the very talented team at Wheeler Bio to help implement a truly innovative model in the biologics CDMO space," commented Lias. "The Wheeler Bio model "democratizes" protein development and manufacture for companies with products at a translational-stage needing to access robust, compliant, and economically viable processes and cGMP capacity in support of clinical development."

Wheeler Bio is a biomanufacturing pioneer, founded by a team of industry experts and strategic investors who believe a different CDMO model is needed to help innovators reach their clinical milestones faster. Wheeler's novel hub-and-spoke operational model, centered in the biomanufacturing metro of Oklahoma City (OKC) and integrated with coastal biotechs and discovery CROs, will revolutionize the speed of drug development. Their technology platform, Portable CMC, simplifies the path between drug discovery and clinical manufacturing by standardizing and democratizing the innovation-to-impact process. A new bridge for translating discoveries to IND filing, innovators benefit from increased momentum during technology transfer, shorter timelines, and lower costs.

Aptar Expands Pharmaceutical Services; Announces Exclusive Collaboration Between Aptar Pharma & Fluidda

Nanopharm, an Aptar Pharma company and leader in contract research and development services for orally inhaled and nasal drug products (OINDPs), recently announced an exclusive collaboration with Fluidda, a leader in the field of Functional Respiratory Imaging. The companies will leverage their respective proprietary technology platforms to help accelerate US FDA approvals for orally inhaled generic products (OIDPs) via the alternative bioequivalence pathway. Nanopharm was acquired by Aptar in 2019, as part of the company's strategy to expand its services offerings and partner with pharmaceutical companies earlier in the drug development process.

Nanopharm has pioneered the development of the alternative bioequivalence regulatory pathway for US FDA approval of generic OIDPs for Asthma and Chronic Obstructive Pulmonary Disease (COPD) using its proprietary in vitro and in silico service platform, SmartTrack. Fluidda's proprietary in silico platform FRI (Functional Respiratory Imaging) delivers quantitative predictions of regional drug deposition in disease-state lungs using Computational Fluid Dynamics (CFD). The FRI platform provides critical information to help understand the availability and activity of the drug at the site of action in the lungs, when complemented by Nanopharm's local lung physiologically-based pharmacokinetic (PBPK) model platform and its in vitro data.

This novel approach is intended to allow pharma companies to file Abbreviated New Drug Application (ANDA) dossiers without the need to perform time-consuming, costly and often unpredictable clinical end-point studies. Similarly, it can support 505(b)(2) filings, by derisking and abbreviating clinical studies.

Having already worked together closely for a number of years, Nanopharm and Fluidda have gained a unique insight into the complex and continually evolving regulatory requirements. This exclusive collaboration deepens the relationship between Fluidda and Nanopharm, benefiting both patients and customers with an uncompromised and holistic approach in developing the scientific rationale to demonstrate bioequivalence using only in vitro and in silico methodologies. The first potential approval of an OINDP using the alternative bioequivalence approach is pending, and, when approved, will further validate Nanopharm's SmartTrack as the go-to solution for alternative bioequivalence studies and should accelerate demand for the companies' collective services.

With momentum building for the transition to new lower global warming potential (GWP) propellants for pMDIs, SmartTrack will also help companies to understand and modulate the impact of these new propellants on drug deposition and dissolution in the lungs, giving confidence in the performance of the reformulated product before embarking on any necessary clinical studies.

Aptar Pharma is part of AptarGroup, Inc., a global leader in the design and manufacturing of a broad range of drug delivery, consumer product dispensing and active material science solutions and services. Aptar Pharma's analytical, laboratory and regulatory services add value at every stage of the drug development process, accelerating and de-risking the program along the way. Nanopharm, an Aptar Pharma company, is a leading provider of specialized analytical and product development services, with a focus on orally inhaled and nasal drug products.

Actylis Debuts, Signaling the Creation of an Integrated Global Specialty Ingredients Manufacturing & Sourcing Powerhouse

Actylis, a leading global manufacturer and sourcing expert of critical raw materials and performance ingredients for the life sciences and specialty chemicals markets, recently made its debut. The new company combines Aceto and 10 industry specialists into an integrated global ingredient powerhouse. Actylis ("Ac-till-iss") is the culmination of an ambitious initiative launched several years ago to address the major unmet need for better and more dependable access to critical raw materials and performance ingredients essential for the manufacture of highly regulated products in key industries.

To achieve this goal, Actylis has integrated leading specialty ingredient manufacturing and sourcing companies, including A&C, A&C Bio Buffer, Aceto, Biotron Laboratories, Cascade Chemistry, Finar, Inter-Actifs, IsleChem, Pharma Waldhof, Syntor Fine Chemicals and Talus into one company. Their breadth of capabilities enables Actylis' unique hybrid manufacturing and sourcing model, which provides key benefits to its customers in high-growth end markets, including pharmaceuticals, agriculture, cosmetics, nutrition, and specialty chemicals.

Gilles Cottier, Chief Executive Officer of Actylis, said "Today we are introducing Actylis, an entirely new and transformed company designed for the challenges and opportunities of the 21st century. Actylis unites multiple industry specialists with a wide range of capabilities into a new, global enterprise with a unique hybrid approach that is greater than the sum of its parts. This consolidation enables us to offer customers across diverse locations and industries highly flexible, customized solutions addressing their specific needs, while assuring reliable on-time delivery of the high-quality ingredients essential to their success."

Actylis was created from the merger of eight specialty manufacturing companies and three sourcing firms, integrated into a single enterprise with more than 850 staff with intimate, in-depth knowledge of every segment they serve. Actylis has a presence in 10 countries spanning three continents and offers more than 4,000 products. With over 75 years of manufacturing and sourcing experience and a portfolio of GMP and non-GMP manufacturing facilities across multiple regions, Actylis offers customers the flexibility to choose from a wide range of individualized solutions, all backed by the same world-class quality, supply chain reliability and regulatory expertise. Its capabilities encompass the entire R&D, product development, and manufacturing spectrum, including technical sales support, R&D, manufacturing and production, quality, supply chain, global sourcing, and regulatory compliance.

Actylis' expert procurement teams, which are strategically located in centers of excellence in key regions across North America, Europe and Asia, represent a major resource for their customers, facilitating product customization and seamlessly addressing customers' needs.

Merck Joins Accumulus Synergy as a Sponsor to Transform the Global Drug Regulatory Submission Process

Accumulus Synergy recently announced Merck, known as MSD outside the US and Canada, has joined Accumulus Synergy as a sponsor company.

"As Accumulus Synergy continues the global journey to drive transformation toward a digital world, I am extremely pleased to have Merck join our mission. Together, we will leverage cloud technology to improve information exchange with and among health authorities in an effort to reduce drug lag for patients around the world," said Frank Nogueira, Accumulus Synergy CEO.

"Merck is a pioneer in developing novel medicines and vaccines and providing access to them around the world. As such, we believe Accumulus Synergy platform is an important industry initiative that creates a way for companies to collaborate with health regulators more efficiently," said Darrel Hicks, Vice President, Global Regulatory Affairs Innovation, Quality and Strategic Operations, who has also been appointed as a Board Member of Accumulus Synergy.

Accumulus Synergy is developing a powerful and secure cloud-based tool to enhance collaboration, data, and content sharing across all regions of the globe. By leveraging technology to modernize the regulatory lifecycle, this tool will enable a dynamic approach that shifts the focus from documents to data that will create significant value for patients, healthcare providers, health authorities, and biopharma companies globally. Accumulus Synergy will implement the highest safeguards and encryptions to ensure that data is appropriately protected in the company's ecosystem, in compliance with countries' privacy laws.

"Our goal is to break new ground in health equity by dramatically accelerating critical therapies to citizens of the world. Accumulus has an excellent and growing team in place, a Board that is today further strengthened by the addition of Merck, and we continue to hire additional staff to meet our platform development objectives. Our non-profit status provides us the ability to work closely with health authorities around the world to support their own data modernization efforts," commented Jeremy Chadwick, PhD, MS, Accumulus Synergy Chairman of the Board and Senior Vice President and Head of Global Development Office, R&D, Takeda Pharmaceuticals.

Accumulus Synergy, Inc. is a non-profit organization formed in 2020 to create a cloud-based platform to transform data sharing between the biopharma industry and global health authorities. The common-platform approach aims to improve efficiencies in the regulatory process by leveraging advanced technology, including data science and AI, as well as tools for secure data exchange to improve patient safety, help reduce the cost of innovation, and ultimately bring patients safe and effective medicines faster. It will work with partner companies, key stakeholders, and global health authorities to build and sustain a platform that meets regulatory, cybersecurity, and privacy requirements spanning clinical, safety, chemistry and manufacturing, and regulatory exchanges and submissions. Accumulus Synergy sponsors include: Amgen, Astellas, AstraZeneca, Bristol Myers Squibb, GSK, Johnson & Johnson, Lilly, Merck, Pfizer, Roche, Sanofi, and Takeda.

SCHOTT Pharma Expands Cartridge Production in China & Hungary

SCHOTT Pharma is again announcing plans to expand its manufacturing facilities: With a double-digit million Euro investment, the company aims to significantly increase its production capacity for cartridges in China and in Hungary.

"Pharmaceutical cartridges are an essential component of injection devices, such as pen, auto, and wearable injectors, that make it easier for the patient to self-administer insulin and other drugs in a home or hospital care setting. This is a growing trend and by expanding our manufacturing capacities, we are supporting the pharma industry in enhancing patient comfort," said Andreas Reisse, CEO of SCHOTT Pharma.

"Pharma companies rely on a supplier with a global production footprint, who can deliver the quantities they need and can optimally tailor its capacity increases to their future business. Already today, we're present in all major regions of the world and the leading insulin providers in Asia and Europe rely on our cartridges," added Frank Bellemans, Vice President for Global Operations at SCHOTT Pharma.

The expansions follow a number of investment announcements, including plans to increase the production capacity of ready-to-use cartridges in Switzerland.

Medical therapies often require patients to receive a drug frequently over a long time, which can impact the lives of the patients tremendously. Pharma companies are therefore looking for ways to enhance patient comfort. This can be achieved by enabling patients to perform the required drug administration themselves using pen or auto injectors. These rely on pharmaceutical cartridges or syringes that combine the capabilities of safe storage and accurate injection of the contained drug.

SCHOTT Pharma cartridges are compatible with a wide range of devices to enable safe and easy-to-use drug delivery in highly accurate doses. As a non-sterile variant, the cartridges are available in 1-20 ml formats and delivered in a tray with optional dividers. The investment will further allow the company to advance its state-of-the-art forming technology and 100% on-line inspection systems.

SCHOTT Pharma designs solutions grounded in science to ensure that medications are safe and easy to use for people around the world – because human health matters. The portfolio comprises drug containment and delivery solutions for injectable drugs ranging from prefillable glass and polymer syringes, to cartridges, vials, and ampoules. Every day, a team of around 4,700 people from over 65 nations works at SCHOTT Pharma to contribute to global healthcare. The company is represented in all main pharmaceutical hubs with 17 manufacturing sites in Europe, North and South America, and Asia. With over 900 patents and technologies developed in-house, a state-of-the-art R&D center in Switzerland, and around 130 employees in R&D, the company is focused on developing innovations for the future. SCHOTT Pharma AG & Co. KGaA, headquartered in Mainz, Germany, is part of SCHOTT AG that is owned by the Carl Zeiss Foundation.

Genelux Corporation Initiates Pivotal Phase 3 Trial Evaluating Olvi-Vec for the Treatment of Platinum-Resistant/Refractory Ovarian Cancer

Genelux Corporation recently announced it has initiated OnPrime, a multi-center, randomized, open-label Phase 3 registrational trial evaluating the efficacy and safety of Olvi-Vec in combination with platinum-doublet + bevacizumab compared to platinum-doublet + bevacizumab in patients with platinum-resistant/refractory ovarian cancer (PRROC).

OnPrime is a US-based trial that will be conducted at approximately 30 sites across the country and has a planned enrollment of 186 women with PRROC, randomized 2:1 into an Experimental Arm of Olvi-Vec and platinum-doublet + bevacizumab and an Active Comparator Arm of platinum-doublet + bevacizumab.

"Initiating the OnPrime trial represents a major milestone for Genelux," said Thomas D. Zindrick, President and CEO, Genelux. "Based on the positive results of our VIRO-15 Phase 2 trial, we believe that Olvi-Vec-primed immunochemotherapy has the potential to address the high unmet need of patients living with PRROC. Our goal in Phase 3 is to replicate these positive results and transform the treatment paradigm for this particularly difficult-to-treat cancer. We look forward to progressing our study and sharing updates on the Olvi-Vec clinical development program."

To date, Olvi-Vec has been studied in multiple early- and mid-phase clinical trials via regional, local and systemic deliveries, as a monotherapy and in combination with other therapies, in approximately 150 patients with a variety of cancer types. In the VIRO-15 Phase 2 trial, twenty-seven PRROC patients with a median of four prior lines and disease progressed after the last prior line, were enrolled. Olvi-Vec met the pre-established efficacy and safety endpoints as shown in data presented in an Oral Plenary Session at the International Gynecologic Cancer Society 2020 Annual Global Meeting. Median progression-free survival by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 was 11.0 months (95% CI, 6.7-13.0 months), overall response rate (ORR) by RECIST1.1 was 54%, and ORR by GCIG CA-125 was 85%. The most frequent grade 3 treatment-related adverse event was abdominal pain (7.4%), with no observed treatment-related discontinuations or patient deaths. Our clinical trials have yielded data that has informed future clinical strategy and trial design involving multiple indications and methods of delivery.

OnPrime Study eligibility: Eligible patients will have a minimum of 3 prior lines of therapy, but there is no limitation on the maximal number of prior therapies. The primary endpoint is progression-free survival based on RECIST 1.1 as assessed by a blinded independent central review, with overall response rate, overall survival and safety as key secondary endpoints.

Olvi-Vec is a proprietary, non-pathogenic oncolytic vaccinia virus, modified to increase its safety, tumor selectivity and therapeutic potential. Virus-mediated oncolysis results in immunogenic cell death and triggers immune activation and memory for long-term immunotherapy against cancer. Olvi-Vec has been administered to more than 150 patients in clinical studies. In these studies, Olvi-Vec was generally well tolerated, and demonstrated evidence of clinical benefit.

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Decibel Therapeutics Announces Submission of IND Application for Lead Gene Therapy Candidate

Decibel Therapeutics recently announced the submission of an Investigational New Drug (IND) application to the US FDA for a Phase 1/2 clinical trial in pediatric patients of DB-OTO, a gene therapy product candidate designed to provide durable restoration of hearing in individuals with profound congenital hearing loss due to an otoferlin deficiency.

DB-OTO is being developed in collaboration with Regeneron Pharmaceuticals and is an adeno-associated virus (AAV)-based dual-vector gene therapy designed to provide durable hearing to individuals with profound congenital hearing loss caused by mutations of the otoferlin gene. The product candidate uses a proprietary, cell-selective promoter to express the otoferlin transgene in hair cells, with the goal of enabling the ear to transmit sound to the brain and provide hearing. In preclinical studies, Decibel observed that local delivery of DB-OTO to the ear resulted in production of otoferlin protein and instatement of auditory brainstem responses to sound in a congenitally deaf rodent disease model. DB-OTO received Orphan Drug and Rare Pediatric Disease designations from the FDA in 2021.

"This submission is an important milestone for the Decibel team as we continue advancing our gene therapy pipeline to address areas of unmet medical need. DB-OTO may potentially provide a new treatment option for children born with otoferlin deficiency, a leading cause of infant hearing loss, for which there are no approved pharmaceutical remedies," said Laurence Reid, PhD, Chief Executive Officer at Decibel. "We look forward to initiating a Phase 1/2 clinical trial of DB-OTO in pediatric patients in the first half of 2023, pending regulatory clearance."

Decibel Therapeutics is a clinical-stage biotechnology company dedicated to discovering and developing transformative treatments to restore and improve hearing and balance, one of the largest areas of unmet need in medicine. Decibel has built a proprietary platform that integrates single-cell genomics and bioinformatic analyses, precision gene therapy technologies and expertise in inner ear biology.

Decibel is leveraging its platform to advance gene therapies designed to selectively replace genes for the treatment of congenital, monogenic hearing loss and to regenerate inner ear hair cells for the treatment of acquired hearing and balance disorders. Decibel's pipeline, including its lead gene therapy product candidate, DB-OTO, to treat congenital, monogenic hearing loss, is designed to deliver on our vision of creating a world of connection for people with hearing and balance disorders. For more information, visit www.decibeltx.com.

Bora Pharmaceuticals Partners With TaiRx to Manufacture Breakthrough Anti-Cancer Drug

Bora Pharmaceutical Laboratories Inc., a division of Bora Pharmaceuticals, has partnered with TaiRx, Inc., a premier Taiwan new drug development company, to manufacture a novel anti-cancer drug, CVM-1118. CVM-1118 is a new small molecule chemical entity being developed by TaiRx as a potential anti-cancer agent in numerous human cancer cell lines with strong anti-cancer activity, high safety margin, and multiple mechanisms of actions in targeting cancer-specific factors.

In particular, CVM-1118 possesses the novel mechanism of inhibiting a unique structure known as vasculogenic mimicry (VM), which is associated with metastasis and drug-induced resistance in malignant tumors. The safety of orally administering CVM-1118 on a human is evaluated from the Phase 1 study US FDA. Based on results of the Phase 1 clinical studies, CVM-1118 obtained the approval to conduct two Phase 2 clinical trials by both the US FDA and Taiwan FDA.

Commenting on the partnership, Bobby Sheng, CEO of Bora Pharmaceuticals, said "We are extremely excited about this new partnership with TaiRx. As a trusted global pharmaceutical partner, we look forward providing many of our technical and quality resources to TaiRx and supporting them on this important project."

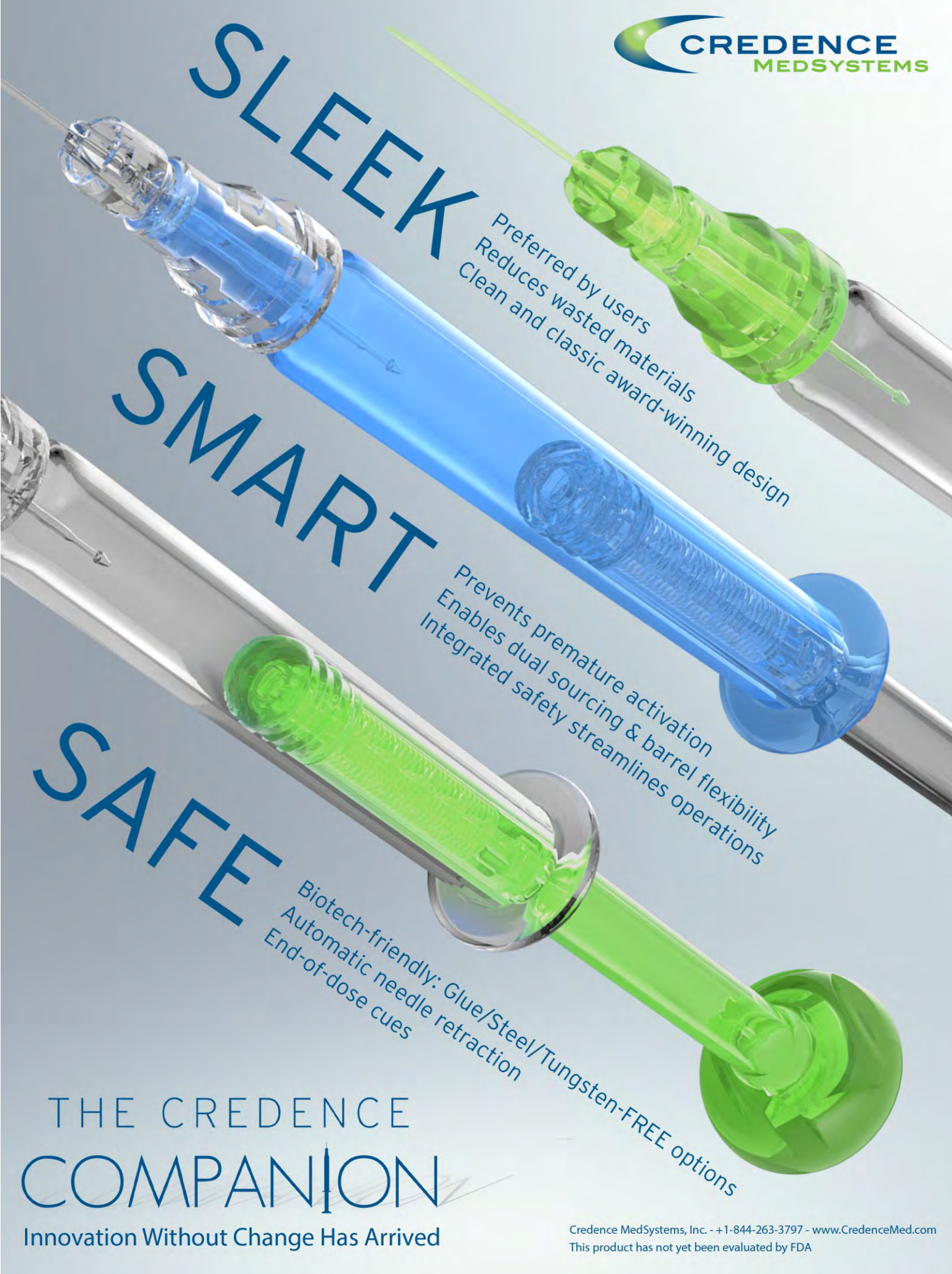
"As we enter the second stage of clinical trials, we hope our success continues and we hope to gain approval from the NDA for CVM-1118 in the near future," added Dr. Du-Shieng Chien, President and CEO.

The manufactured batches will be used to further support Phase 2 clinical trials and then submitted to the NDA for approval. Bora Pharmaceuticals' sites already have an excellent track record with many regulatory agencies around the world including the USFDA, MHRA, TFDA, ANVISA, Health Canada, and many others.

Bora Pharmaceuticals recently announced it acquired a $100-million Biologics site in Taiwan as part of its 5-year growth plan. The investment enables Bora Pharmaceuticals to significantly expand its capabilities in the Biologics space, which will allow its customers to gain access to high-quality manufacturing facilities for their new and innovative pharmaceutical products.

Bora Pharmaceuticals is a premier international CGMP CDMO specializing in complex oral solid dosage, non-sterile liquids, nasal sprays, and semi-solids 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. Our TAA-compliant sites deliver to more than 100 markets around the world, including the US, Canada, EU, Southeast Asia, Middle East, and South and Central Americas. Bora handles high potency compounds, solvents, flammables, and IR/SR/ER release profile products.

TaiRx, Inc. was founded in 2011, a Taiwan R&D based pharmaceutical company with global talents focusing on a new generation of oncology molecule for Asian and global markets. TaiRx has a rich product pipeline and many of products are moving rapidly into various clinical stages to ensure the safety and efficacy of the drug products. TaiRx has profound global drug development knowledge and experience to expedite the drug development process.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MEDICAL DEVICE TESTING

Chemical Characterization & the Non-Targeted Analysis of Medical Devices

By: Luminita Moraru, MSC, MRSC

INTRODUCTION

At Medical Engineering Technologies Ltd. (MET), we are conducting a variety of Medical Devices Testing. Chemical Characterization is vital for new medical devices released on the market. When a new medical device (MD) is developed, it is mandatory to know the potential effects that this can have on the patient. In addition to the materials of construction there are other products that can be used during cleaning, processing, and sterilization of the devices. These materials can be easily missed from further investigations; the focus is mainly on the materials of construction. Any contaminants or impurities are referred to as Non-Target Materials (NTMs). When chemical analysis is performed, it is important that screening methods are developed to detect all potential extractables and leachables, rather than only target materials.

The scope of the medical devices is to monitor, diagnose, or treat an injury or medical condition, or to prevent and monitor a disease. There are many medical devices being designed every day, such as insulin pumps, syringes, oxygenators, diabetic pens, heart valves, brain implants, dental implants, etc.

At MET, we are specialized in developing bespoke ISO 10993-18 extractables and leachables studies for a whole range of these devices. Medical Devices can be categorized by the duration of body contact (eg, =1day, >1 to 30 days, or >30 days), frequency of body contact (eg, continuously versus intermittently), and type of body contact (eg, surface contact with intact skin, mucosal contact, implantation in tissue, or intravascular implantation) according to ISO 10993.

The investigation of the potential risks is developed based on the information provided by the manufacturer of the device, components, and materials.

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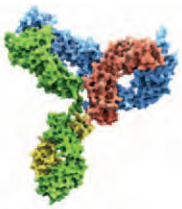

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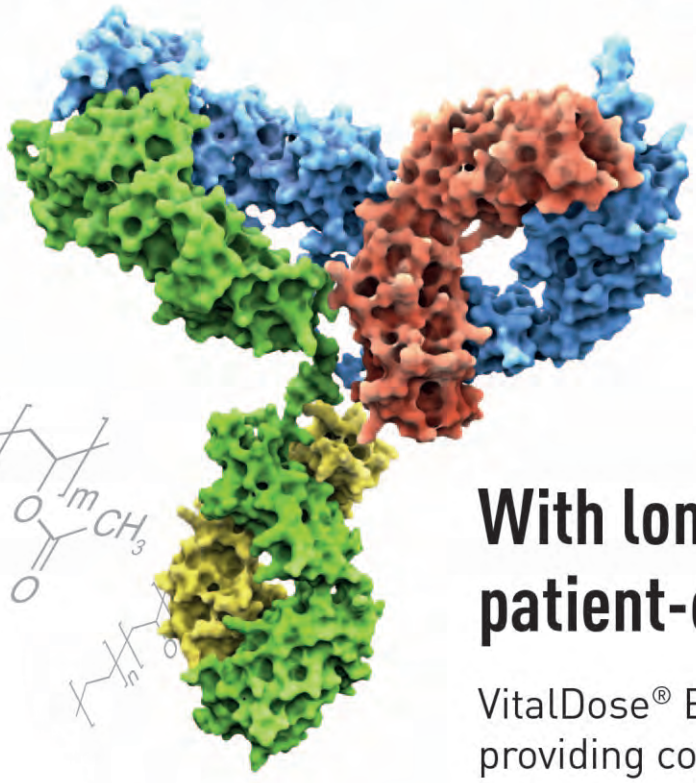

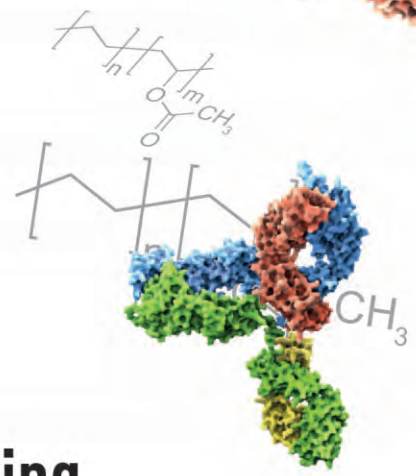

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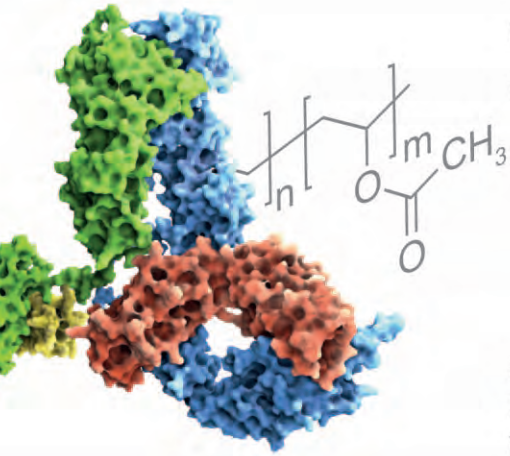

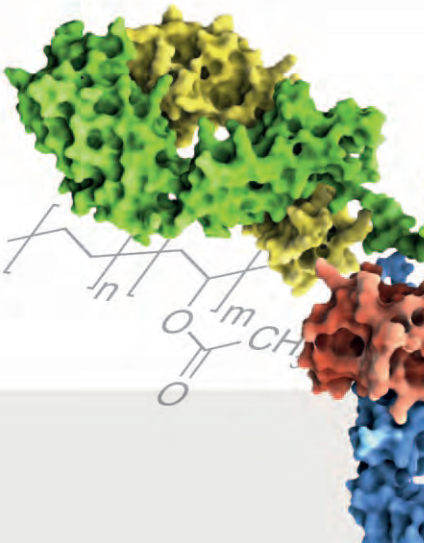

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INFORMATION GATHERING

Information Gathering is the crucial first step in testing MDs, and this is covered by the Biological Evaluation Plan (BEP), which is a risk assessment and gap analysis (as per ISO 10993-1 Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process), detailing all the materials that the medical device is composed of and the potential risks that the patient could be exposed to. The BEP includes a review of the existing scientific information, and it can lead to new testing to determine if the device is safe for the intended use. Based on the information provided in the BEP, the testing study is designed.

Depending on the contact route of the MD, further tests covered by ISO 10993: Biological Evaluation of Medical Devices for direct contact devices or ISO 18562: Biocompatibility evaluation of breathing gas pathways in healthcare applications are recommended.

CHEMICAL ANALYSIS

This is performed in accordance to ISO 10993 series and involves a broad range of studies, designed specifically for each product. Extractable and leachable studies are mostly used to assess direct-contact MDs. For example, implant devices, due to their permanent duration of contact in the tissue, and where any potential degradation is possible must be evaluated for any potential degradation, and the degradation products must be analyzed. Extractable and Leachable studies are designed according to ISO 10993 parts 12 & 18, whilst degradation studies follow parts 13, 14, and 15, depending of the materials of construction.

Extractables are materials that can be extracted from the MD during exaggerated and accelerated conditions. The accelerated conditions are simulated by increasing the temperature of the extractions, eg, for an MD with an intended use at body temperature, the exaggerated extraction will be performed at a higher temperature, such as 50°C. Extractable compounds can be forced out from the MD using aggressive solvents. The extraction vehicles are chosen considering the intended use, exaggerating the polarity of the solvent, temperature, and extraction time, without dissolving the product. When choosing the extraction vehicles, ISO 10993 suggests that the scope is not to dissolve or compromise the device, so the selection of the extraction conditions must be well-evaluated prior to testing and the selection justified.

Leachables are the compounds that can leach from the device under normal use conditions; this process is generally performed by simulating the normal use of the MD. When it comes to assessing the leachable compounds, it is important to recreate the biological environment of use and, if formulations are present, to use the drug vehicle or fluid that the device will be contacting during use. It is mandatory to assess the MDs for leachable compounds, as these possess a high risk to the patient. Leachable compounds are transferred in the body by the drug and could lead to reactions that can harm the patient.

In addition to extractable and leachable testing, implant devices, where there is a potential for degradation, must be assessed for any degradation products. The degradation studies are intended to simulate the complex environment in the body; they are performed using hydrolytic and oxidative solutions.

It is important to know that the accelerated degradation uses high temperatures, and the extraction solutions must be analyzed over specific periods of time (given in the standard or justified in the testing protocol). However, it can be challenging to use this approach to identify all the hazards present and released by the devices, due to the complexity of the materials and different manufacturing processes. For example, complex devices can introduce chemicals that are not accounted for by formulation information solely.

To cover the gaps, MET is conducting targeted and non-targeted screening analysis using a variety of analytical techniques in order to investigate any residual impurities that could be volatile, semi-volatile, non-volatile, organic, or inorganic that are present at concentrations above the AET (Analytical Evaluation Threshold).

The studies are developed bespoke for each product. They consider worst-case scenarios of release of materials by the device. The selection of extraction media and conditions and the instrumentation used is based on sample proprieties, the chemical make-up, and the application of the device.

At MET, we have a broad range of analytical techniques available:

- Head Space-Chromatography coupled with Mass Spectrometry (HS-GC-MSD) is used to screen and identify any potential volatile organic impurities or residual solvents released by the MD or from the manufacturing process that could harm the consumer. HS-GC-MS may be performed on an aqueous extract or directly on a solid test article.
- Gas chromatography coupled with Mass Spectrometry Detection (GC-

MSD) methods are developed to search for a multitude of potential semi-volatile impurities that could be released by the device. These may derive from the manufacture and storage of polymers and precursors or be added (purposely or inadvertently) during the manufacturing, sterilization, or any other treatments of the raw materials, components, or device. The extract media is normally introduced into the analytical equipment by direct injection.

- High Performance Liquid Chromatography methods with Photodiode Array Detection coupled with Mass Spectrometry (HPLC PDA-MSD) detection are developed based on the material of construction of the MD and the potential non-volatile residuals that could harm the user. The dual detection method PDA and MS is designed to have a higher sensitivity, as it has the capability to detect organic compounds that do not ionize and contain chromophore groups (such as colorants or monomers added to the devices) and molecules that can ionize.
- Inductively Coupled Plasma Optical Emission Spectroscopy (ICP-OES) is used to search for any potential non-organic (metallic) residuals left behind from manufacturing machinery or from any metals or pigments associated with the MD.

Materials can be quantified by using either targeted (fully quantitative) or non-targeted (semi-quantitative) methods. Targeted quantification refers to the analysis of a specific analyte or a group of analytes of interest using pure reference standards within a defined concentration range. To evaluate analytical suitability for use in quantification, a calibration curve is produced with 5 to 6 non-zero calibration points.

System suitability is the assessment that is used to determine the performance range of the analytical instrumentation prior to testing. The system suitability assessment determines whether the method has been implemented properly, maintains its performance at the same level as during qualification, and performs acceptably throughout its use. System suitability for NTM work has been proposed to include the use of blanks, pooled samples such as matrix controls, and multi-analyte-spiked (with reference/control materials added) samples. The selection of the reference or target materials is based on prior information and is used to perform calibration and system suitability analysis.

Analytical Evaluation Threshold is defined as the level below which quantification of a material is not required; the analyst doesn't need to identify, quantify, or report peaks for toxicological risk assessment. The AET was adapted for MDs in the 2020 edition of ISO 10993-18. The calculation of the AET considers the dose-base threshold (DBT), which depends on the frequency and duration of a patient's exposure to a device, as described in ISO/TS 21726:2019. It should be noted that, according to ISO 10993-18:2020, AET is not applicable to substances named as "cohorts of concern." These materials are considered highly toxic at very low concentrations, such as volatile organic compounds and non-organic compounds. Therefore, AET is only valid for semi-volatile and non-volatile organic com-

pounds and is calculated as AET = (DBT x (A/(B x C)))/UF.

A is the number of devices extracted, B is the extract volume, C is the number of devices that contact the body divided by 1 day, D is the dilution factor, and UF is the uncertainty factor of the analytical method. The value of the UF depends on the analytical method and accounts for variation in the response factors (RFs) of individual analytes.

As most of the time the test extract fluid sample goes through multi-step preparation, including concentration and dilutions, a D factor must be considered (D<1 where the sample is concentrated and D>1 for diluted samples).

Once extracts of the devices are obtained, the solutions prepared (diluted, concentrated, etc) are injected into the systems; analysis involves separation of the molecules extracted using the aforementioned methods.

EXTRACTIONS

The extraction process is intended to transfer mobile chemical constituents from the MD into a liquid phase/solvent. The extractions can simulate the real-life or worst-case scenarios, with respect to clinical use.

The selection of the solvents is made from a broad range of candidate organic solvents. The goal is to cover all the polarities that are clinically relevant. The extractions are conducted on patient-contacting devices/components to result in a worst-case scenario, with respect to the clinical use.

Solid-liquid extraction is not the only possibility; liquid-liquid extraction applies when the device is in a liquid form and gas to solid phase extraction (followed by return release to gas for analysis) applies for breathing components.

The extraction process is controlled by the interaction of the device or material with the extraction vehicle (solvent) and is governed by the solubility, diffusion of the chemical into the solvent, and partitioning of the chemical between the solvent and the material, extraction temperature, extraction duration, and surface area. The goal of the extraction is to facilitate migration of chemical constituents that could potentially leach out of the device during clinical use without changing their chemical identities or physically destroying the device.

In some cases, exhaustive extraction is required (for example: in the case of implanted devices). This is defined as repetitive extraction, performed until the amount of material extracted in a subsequent extraction step is less than 10% (by gravimetric analysis of that determined in the first extraction step). The most common method for checking is to assess the Non-Volatile Residue (NVR) analysis.

This method is relatively simple; however, the approach is limited by the sensitivity of gravimetric analysis and is insensitive to volatile and some semi-volatile compounds.

When a device is invasive but not permanent, exaggerated extraction may be appropriate. This is performed by the use of solvents and temperatures that represent a worse case than the conditions of the clinical use (temperatures chosen above 37°C and extraction duration longer than the duration of the device use).

Because clinical use of a device can extend over a considerable time period, accelerated extraction is used to allow analysis to be performed in a reasonable timescale. This is defined as an extraction with a duration shorter than the duration of the clinical use, whilst not causing degradation, chemical, or physical changes to the substances being extracted. The accelerated extraction is usually achieved by increasing the temperature used.

When selecting materials and components for use in an MD, designers will pay attention to the biocompatibility of these items. However, final proof of biocompatibility must be given for the device presented to the patient. Therefore, the selection of the test article for the study is very important. The study aims to replicate the real use of the product and it must, therefore, be representative of the final product (as opposed to a raw material, resin, or unfinished medical device).

In targeted analysis, the chemistry of the extractable of interest is known, allowing extraction optimization. In NTAs, however, the chemistry of each potential extractable is typically unknown and varies. Therefore, to maximize the extraction of chemicals having a broad range of chemistries, non-targeted extraction conditions usually include the use of polar, semi-polar, and non-polar solvents, elevated temperature, and longer extraction times.

The polarity selection of the solvent is performed as per Table D.1 of ISO 10993-18:2020. The selection of polar, semi-polar, and non-polar solvents is recommended for devices intended for long-term use (>30days). The selection of the solvent must also consider the tissue the device will contact, in order to simulate the worst-case scenario.

One example would be alcohol-water mixtures that can have polarities in the semi-polar to non-polar range. Extractions using alcohol-water mixtures can result in

lower concentrations of extractables and can underestimate their presence in comparison to extractions purely using alcohol.

Another important parameter in extraction study design is the solvent volume-to-sample size ratio. Concentration or dilution of the extract is performed with consideration of the reporting limit and the sensitivity requirements of the analytical techniques used for extractable profiling .ISO 10993-12:2021 contains recommendations for various ratios of the device surface area or mass-to-solvent volume, depending on the device characteristics, and ISO 10993-18:2020 contains recommendations to use these ratios as potential starting points in planning an extractables study. However, the final solvent volume determination is based on factors that include the properties of a device/material and the extraction techniques used. For example, absorbent materials will require additional extraction fluid.

It is important that extracts, once generated, are compatible with the analytical methods. The analytical methods must be adequately sensitive and achieve the necessary reporting limit can support a biocompatibility evaluation. In many cases, extracts can be directly analyzed using GC and liquid chromatography (LC) techniques without further sample processing. However, further processing of the samples is often required for analytical instrument compatibility and reliable analytical outcomes. For example, sample dilution, sample concentration, liquid-liquid extraction (solvent exchange), and solid phase exaction (SPE) are some of the techniques used to process the sample extracts prior to injection in the analytical systems.

The need of chemical characterization and toxicological risk assessment for evaluating and supporting the biocompatibility of MDs is constantly increasing. The design and performance of the suitable chemical analysis depends on the collaboration of the team of experts in areas including MD manufacturing, analytical chemistry, and toxicology.

Medical Devices industry is in continuous growth, and the development of new reliable and accurate approaches in order to assess the safety of the products is constantly reviewed. ◆

REFERENCES

1. Chemical Characterization and Non-targeted Analysis of Medical Device Extracts: A Review of Current Approaches, Gaps, and Emerging Practices - Eric M. Sussman,* Berk Oktem, Irada S. Isayeva, Jinrong Liu, Samanthi Wickramasekara, Vaishnavi Chandrasekar, Keaton Nahan, Hainsworth Y. Shin, and Jiwen Zheng.
2. ISO10993-1 ISO 10993-1:2018: Biological evaluation of medical devices — Part 1: Evaluation and testing within a risk management process.
3. ISO 10993-18:2020: Biological evaluation of medical devices — Part 18: Chemical characterization of medical device materials within a risk management process.
4. ISO10993-12: Biological evaluation of medical devices: Part 12: Sample preparation and reference materials.
5. ISO 10993-17:2002: Biological evaluation of medical devices — Part 17: Establishment of allowable limits for leachable substances.
6. ISO 10993-13:2010: Biological evaluation of medical devices — Part 13: Identification and quantification of degradation products from polymeric medical devices.

BIOGRAPHY

Luminita Moraru is the Analytical Chemistry Manager at Medical Engineering Technologies Ltd, has more than 6 years of experience in Medical Devices Testing. She is a committee member of ISO10993: CH/194 Biological evaluation of medical devices and ISO18562: CH/121/09 Lung Ventilators & Related Equipment having insight knowledge for in the applications of those on medical devices to meet the requirements, ensuring the data is generated in appropriate form to be risk assessed in Toxicological Risk Assessments. She earned her Masters in Chemistry at the University of Bucharest.

Drug Development
EXECUTIVE

Michael Earl

Director, Pharmaceutical Services

Owen Mumford Ltd.

Steven Kaufman

VP for Drug Delivery Systems

Stevanato Group

Owen Mumford & Stevanato Group: Collaborating to Produce Aidaptus® Auto-injector

Owen Mumford and Stevanato Group recently signed a deal to collaborate on the production and commercialization of Owen Mumford's innovative Aidaptus® auto-injector. Various benefits arise from combining their expertise. While Owen Mumford boasts expertise in device design, development, and production of drug delivery devices, Stevanato Group provides capabilities in component moulding, as well as sub-assembly and final assembly equipment, to provide its pharma customers with flexibility and confidence for their combination product development.

Drug Development & Delivery recently interviewed Michael Earl, Director of Pharmaceutical Services at Owen Mumford, and Steven Kaufman, Vice President for Drug Delivery Systems at Stevanato Group to discuss their collaboration in producing the innovative Aidaptus auto-injector.

Q: Why did Owen Mumford Pharmaceutical Services (OMPS) and Stevananto Group (SG) decide to collaborate?

Michael Earl: The launch of Aidaptus as our latest innovative auto-injector presented OMPS with an exciting and unique opportunity, but also created some potential challenges for us. The market for disposable auto-injectors has shown significant growth in recent years due to a variety of market trends, such as an aging population with chronic diseases, the shift to remote patient treatment and self-administration,

accelerated by the pandemic, and an increase in subcutaneous injection as a route of administration. So, while the size of the opportunity was apparent, we needed to ensure we could maximize this opportunity and be able to meet the potential demand for the product. We realized a collaboration with SG would provide the means for capacity scale up more flexibly than our own initial capabilities, while allowing us to expand our customer reach across the globe. We knew the collaboration would also provide our customers with assurance of our ability to manage supply of devices optimally, as partners, using the substantial combined resources available to us.

Steven Kaufman: From an SG perspective, the opportunity to be the exclusive partner on the manufacture of Aidaptus provided a perfect fit with our own core capabilities around precision plastic injection moulding and also gave us the opportunity to leverage our expertise in engineering and automation systems by offering sub-assembly and final assembly equipment. And of course, we can also offer customers a range of drug containment solutions for use within the device for both 1-ml and 2.25-ml prefilled syringes. Our global commercial footprint allows us to effectively amplify the Aidaptus sales and marketing efforts led by OMPS to identify more customers who have a need for such a device. OMPS and SG have many shared values and ways of conducting business that are critical to a successful collaboration.

Q: What does OMPS contribute to the collaboration?

Michael Earl: At OMPS, we have a long history designing, developing, and manufacturing auto-injectors, in fact we designed the first auto-injector, Autoject 1, and brought it to the market back in the mid 1980s. Since then, we have made a variety of different reusable and disposable auto-injectors for many pharmaceutical companies both small and large, including supplying the auto-injector for a world leading immunology treatment. So, we have proven expertise in supplying these products at scale over a sustained period of time. We were able to use this extensive knowledge of auto-injectors to help design Aidaptus as a true platform auto-injector and include unique features we believe will really benefit both pharma companies and their patients. We created Aidaptus with a wide design envelope that was subsequently demonstrated in our design verification testing, which showed its ability to work with a range of formulations, needle sizes, and primary containers, providing pharma companies with true flexibility.

Q: What are SG plans with respect to bringing the collaboration to life?

Steven Kaufman: First, at SG we are excited to be involved as exclusive partners in such an innovative product from such an early stage of its commercialization. During the first phase, SG will provide precision plastic injection moulding services for Aidaptus components. We will also leverage our expertise in engineering and automation systems by offering sub-assembly services using equipment designed by our in-house automation team, and in addition, final assembly equipment from benchtop units to high-volume production can be provided as needed by our pharma customers. The sub-assembly equipment will be installed at both SG and OMPS production sites for dual sourcing options. Our commercial team will also work closely alongside the OMPS commercial team to help develop new customers and support existing ones. And with our sites in Europe and the US, we can also provide analytical services, especially related to drug containment solutions.

Q: What are the time-lines for the scale up of the Aidaptus auto-injector?

Michael Earl: Both parties are making investments now in building the capacity. We aim to have a capacity of several hundred thousand units in the coming months with a scale up to several million by 2024. For OMPS, the new assembly equipment will be installed at our new state-of-the-art facility in Witney, UK, which is due for completion in 2023. The Witney site has been designed in accordance with BREEAM certification environmental standards and as such, employs sustainable construction, operation, and design, so it fits well with our company sustainability objectives.

Q: How does the collaboration benefit pharma companies?

Michael Earl: Aidaptus is a true platform auto-injector, so we believe even if the drug formulation changes, the device does not need to. This obviously has advantages in reducing the work and risk associated with changes in formulation, such as additional verification testing, human factors studies, and regulatory documentation. This will all help to reduce time to market for the final combination product, a key element in today's competitive marketplace.

Steven Kaufman: The combined resources, expertise, and manufacturing capabilities of OMPS and SG will help reduce complexity, reduce time-to-market, and minimize supply-chain risk and simplify final assembly for our pharma customers, and together, we can provide a true end-to-end solution for those customers who require more than just a device. In summary, we are hoping to reduce risk in our customers' combination product development. And we help to ensure this by working together to offer greater support to pharma customers who have been looking for viable alternatives to "platform" auto-injectors that are well known to the market today. With both SG and OMPS offering this 1-ml and 2.25-ml hybrid device in a relatively compact form factor, we see several experienced pharma customers starting to evaluate features such as the adaptable plunger rod to support a range of fill volumes.

Q: What makes Aidaptus unique as an auto-injector?

Michael Earl: Aidaptus' innovation lies in its unique design, allowing it to accommodate both 1-ml and 2.25-ml in the same compact-size base device, plus using its patented auto-adjust plunger technology, Aidaptus provides more flexibility as it has the ability to adapt to different fill volumes and plunger positions, without the need for any change parts. This essentially means the same device can be used irrespective of formulation changes that we know can frequently take place during drug development and also as part of life cycle management. So, this can help to reduce risk for our pharma partners as well as reduce time to market in combination product development.

Q: How does Aidaptus help patients?

Michael Earl: Aidaptus has a unique design that means it is simple and intuitive to use with clear visual and audible indicators, and yet the device remains compact in size (161 mm x 18.5 mm). This simplicity means the device can help facilitate self-administration for patients in the comfort of their home setting and at the same time, potentially reduce the need for visits with healthcare professionals, therefore saving time for all. Our approach to the human factor studies ensured the device could be used successfully by a range of intended users so that we are confident it can be used in a variety of therapeutic areas.◆

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EXCIPIENT COMPACTION STUDY

Developing a Reliable Controlled-Release Polymer Using a Compaction Simulator

By: Gopeshkumar Singh, MS, and Ajit Bhagat

INTRODUCTION

To keep pace with pharmaceutical industry trends, drug developers are looking to save time, improve efficiency, reduce cost, and respond quickly to market changes. Understanding the various techniques of continuous manufacturing processes is critical to developing robust, stable drug formulations. The study of polymer behaviors in the presence of various adjuvants and flow aids plays an important role in formulation development, stability, tensile strength, and efficacy with respect to final dosage forms. This is especially true for controlled-release formulations.

Controlled-release tablets help improve patient compliance and therapeutic outcomes. These dosage forms last longer, which reduces dosage frequency. And, because the active pharmaceutical ingredient (API) is released more slowly, there is a decreased chance of noticeable side effects. Depending on the manufacturers' desired drug-release profile, formulators have several advantages to consider when developing controlled-release tablets.

Drug manufacturers can simplify the production of controlled-release tablets by using direct compression. Granulation is a time-consuming technique that, while effective, can lead to product cross-contamination and product loss during processing. In fact, granulation is more costly than direct compression in terms of both time and expense. Direct compression, on the other hand, is a simple and effective way to produce tablets. A manufacturer can blend an API with excipients, followed by compression, which makes the product easy to process. No additional steps, such as drying or sieving, are required. But not all excipients hold up well during this process, which makes the selection of ingredients even more critical.

By using METHOCEL™ (Hypromellose) polymeric excipients in oral solid dosage matrix tablet formulations, quality, value, and robust physical properties attributes can be achieved. These polymers, which have been used in the industry for 70 years, are used in a wide range of applications, such as immediate-release, controlled-release, coating wet granulation, and direct compression. Advanced polymeric excipients are available in various grades based on viscosity and can be a substitute for different ingredients. The water-soluble polymer offers exceptional flexibility and a broad range of properties typically not found in other water-soluble polymers, making it an ideal candidate for continuous manufacturing.

Continuous manufacturing is on the rise and helps manufacturers lower production costs and time, while increasing margins. The process has become a massive resource-saving technique in pharmaceutical manufacturing. Maintaining quality and consistency in continuous manufacturing batches improves drug efficacy. In matrix-controlled-release applications, direct compression can be an effective, affordable option. METHOCEL™ DC2 can be used to modify particle morphology, resulting in improved power flow without the use of additives. These advanced polymeric excipients can be used to modify particle morphology to improve power flow without any additives, resulting in excellent processability when it comes to improved content uniformity and tablet weight, at elevated tablet press speed. Tablet tensile strength is another essential consideration with respect to ingredient compatibility. Products must possess the appropriate strength to avoid crumbling or chipping throughout all stages of delivery.

The pharmaceutical industry continues to focus on the inno-

vation of models or processes that can help predict polymer and API behavior under various processing conditions. By facilitating a compaction simulator, formulators can use the research results to better understand how these processes work using various formulations and compaction weight and learn what to expect when a powder is being pressed into tablets. Being able to adjust nimbly and accurately using a variety of processing methods helps formulators stay ahead of shifting manufacturing trends.

PRODUCTION PROCESS

Hypromellose is a widely accepted polymer for controlled-release applications; it provides the flexibility needed for formulation scientists to modulate drug release for desired therapeutic effect and duration. This study evaluates a compaction simulator to understand the compatibility of polymers, and the effect of tableting pressure on polymer's physical properties.

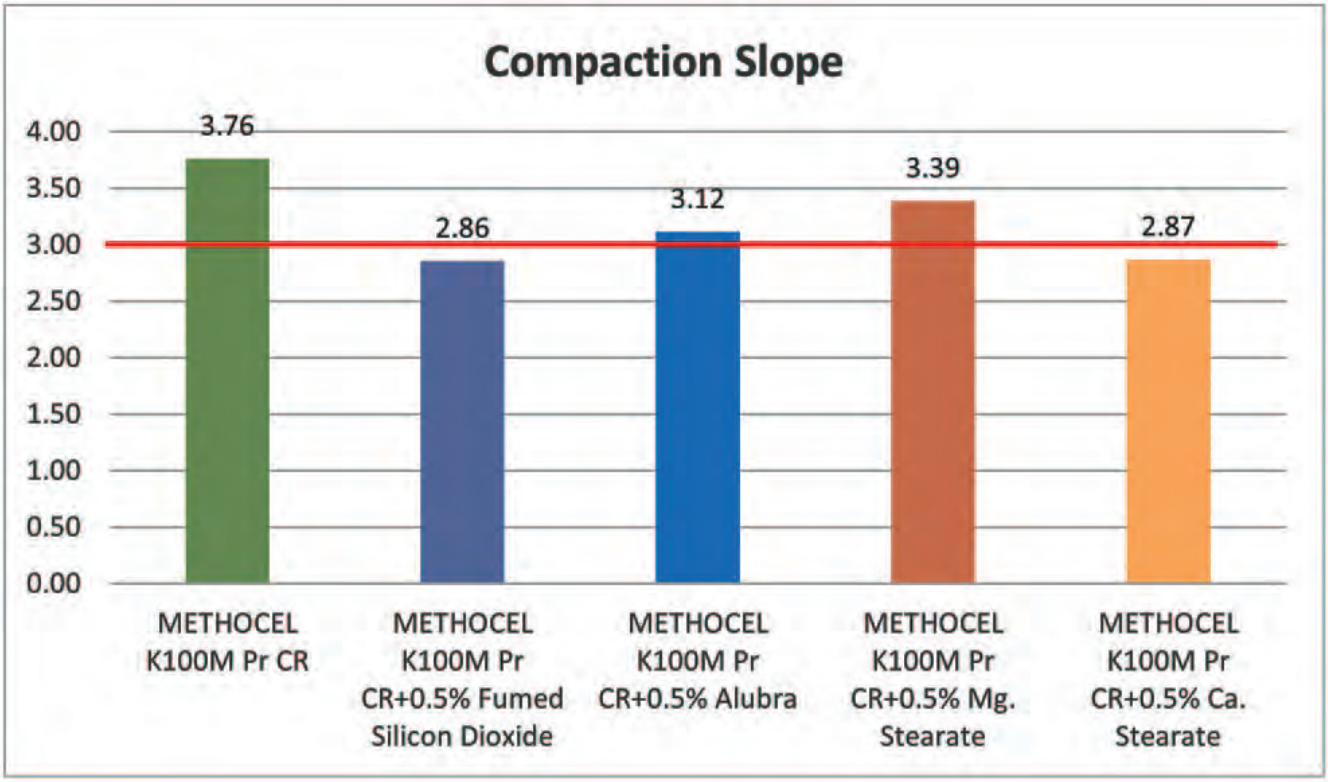
The compaction simulator is designed specifically for a detailed study of the compaction characteristics of powder, while simulating the tableting process using different makes/models of tablet compression machines. The simulator helps formulators understand the compaction process in-depth and helps scientists overcome challenges during scale-up stage. The powder is then compressed into tablets at multiple production speeds using the simulating feature. The simulator uses automatic Heckel analysis and automatic Energy and Power analysis to measure various parameters, such as applied pressure, compression pressure, yield pressure, and more. These features help simulate the tablet machine at manufacturing level and compress the tablets in a predictive pattern to avoid future manufacturing challenges.

This study focuses on the compatibility study of METHOCEL™ K100M Pr CR using an ESH Compaction stimulator from Pheonix Materials Testing Ltd., along with commonly used adjuvants or flow aids under various compaction pressure. The effects of various parameters –such as compaction forces, tableting pressure, tensile strength, and ejection force on compacts – were also investigated.

METHODOLOGY

The advanced neat polymer – with adjuvants such as Calcium Stearate, Magnesium Stearate, or fumed Silicon dioxide – was used to conduct blend studies that contain sets of 5 sequences; each sequence contains 5 tablets. They were sifted through 60 mesh, with material blended in a 0.5-L capacity conta blender for 5

FIGURE 1



Compaction slope of Hypromellose and with Blend of Adjuvants.

minutes at 15-16 rpm.

For each set of the experiment, the compact weight was kept at 500 mg. For adjuvants, 0.5% w/w of the tablet weight was taken and blended with a polymer for further study. Approximately 500 mg of polymer or polymer blends was filled in a 13-mm D type flat surface single punch on the Compaction Simulator. The parameters of each tablet, including hardness, diameter, thickness, and tablet weight, were recorded. The data was then fed to compaction simulator software, which utilizes Heckel analysis and compaction slope, compaction force, tableting pressure, and ejection force, and then recorded.

RESULTS & DISCUSSION

As the simulator uses Heckel analysis, the significance of Heckel constant k is related to the reciprocal of the mean yield pressure, which is the minimum pressure required to cause deformation of the material under compression. A large value of the Heckel constant indicates the onset of plastic deformation at relatively low pressure.

The compaction simulator produces a compaction slope for each set of the experiment and extrapolates the slope at two compression forces, such as @85 mPa and @100 mPa. The higher the slope value, the better material compatibility is seen; the various parameters were noted, including compression force, applied pressure, hardness, and tensile strength.

Compaction Slope

Here, the compaction simulator produces a compaction slope for each set of the experiment. As shown in Figure 1, the advanced neat polymer had the highest slope value, indicative of excellent compatibility.

Per the literature, the higher the compaction slope of a Heckel analysis, the lower the pressure it requires for compaction. The advanced neat polymer shows the highest slope, ie, more than 3.0, which is indicative of low yield pressure to start the deformities of polymer structure, resulting in improved material compatibility.[1]

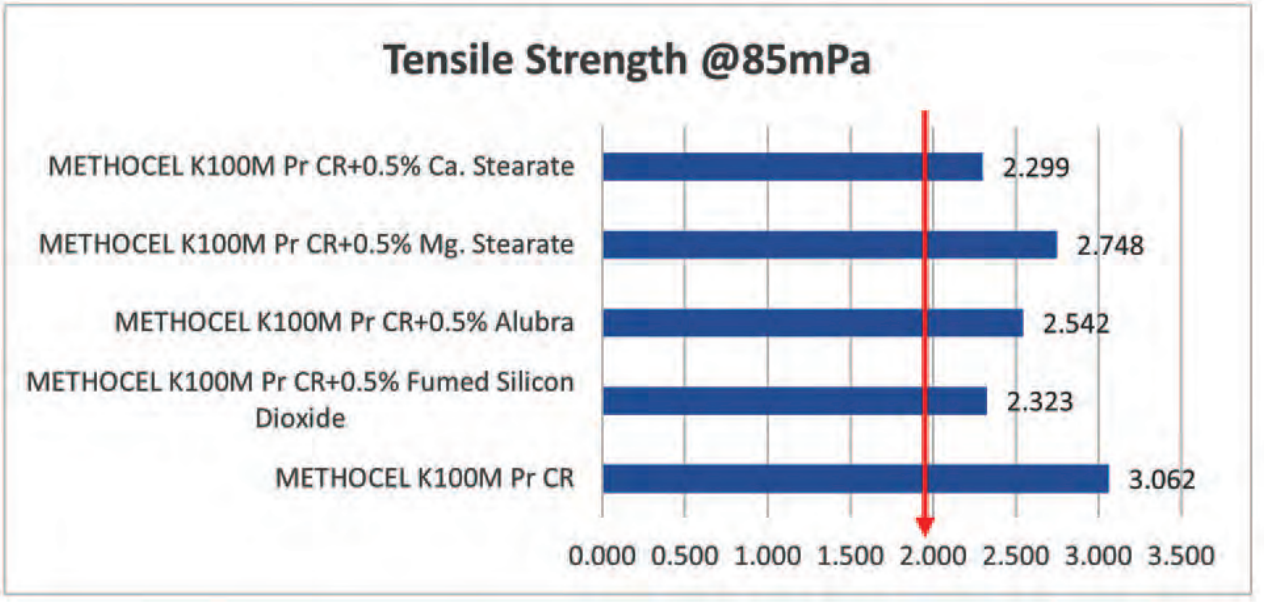
Tensile Strength

Excipients, such as diluents, fillers, and binders, play a significant role in improving a formulation's content uniformity, as well as the resulting tablet's tensile strength. High- dose tablets may lack sufficient tensile strength if the API is not easily compressible, while low-dose formulations may be difficult to blend uniformly.

For small-scale manufacturing, generally, tensile strength should be more than 1 mPa. For commercial-scale production, tensile strength should be more than 1.7 mPa to sustain the down processing, such as tablet coating or packaging.[2] This study indicates tablets produced with Hypromellose have the highest tensile strength (more than 2.0 mPa) to sustain various down processing steps.

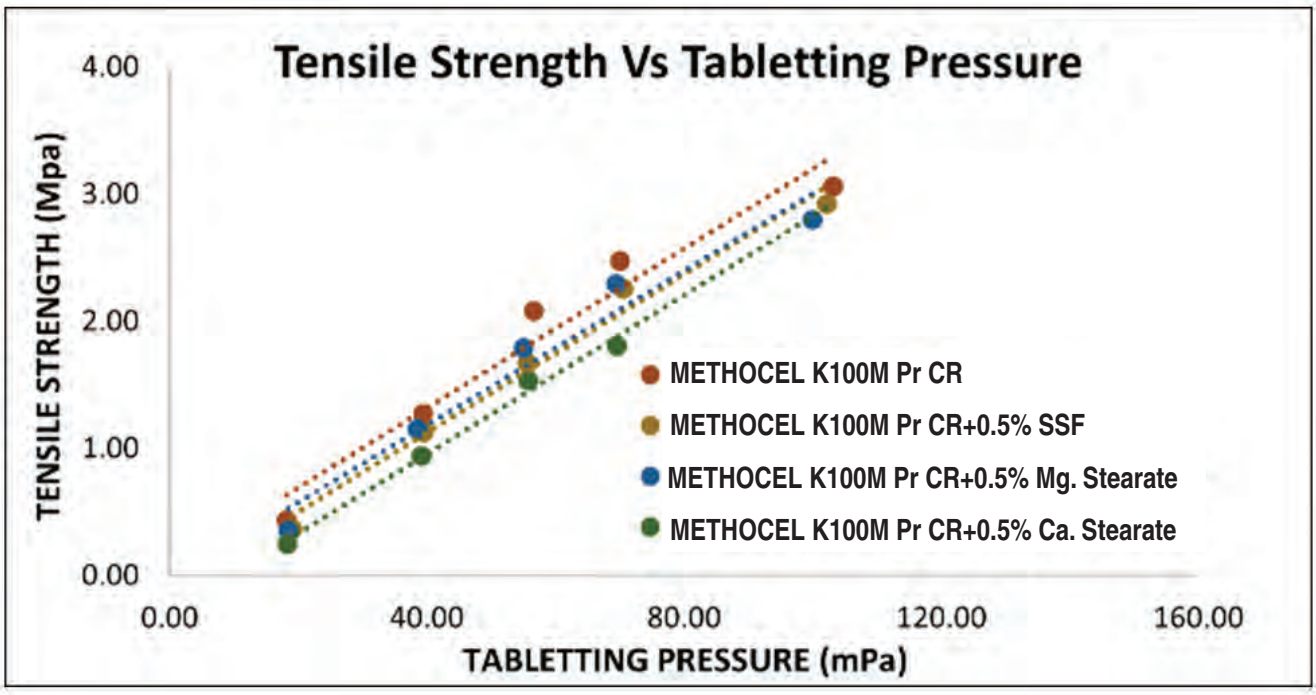
The EHS Compaction simulator extrapolates the data and calculates tensile strength of polymer/polymer blend @ 85 mPa.

FIGURE 2



Tensile strength of Hypromellose and Blends @85 mPa.

FIGURE 3



Tensile strength of tablet at various tableting pressure for Hypromellose and compact blend of Magnesium Stearate, Calcium Stearate, and Sodium Stearyl Fumarate (SSF).

Tableting Pressure Versus Tensile Strength

The machine automatically selects different tableting pressures based on the polymer and blend properties. During compression, the polymer and its blend are subjected to increasing applied and compression pressure. The advanced neat polymer shows good compatibility at all pressures without any tableting issues. Figure 3 highlights a plot comparison between tableting pressure and tensile strength. For most of the combinations, there were no tableting issues – such as chipping, capping, friability observed – except for Magnesium Stearate at higher tableting pressure. The polymer and its blend were able to sustain the higher tableting pressures.

Hypromellose with a flow aid, such as magnesium stearate, calcium stearate, and sodium stearyl fumarate (SSF), showed an improved, higher tensile strength. At higher tableting pressure, SSF was found to produce good compaction, whereas Calcium Stearate @100 mPa tableting pressure experienced chipping and capping (Figures 3 & 4).

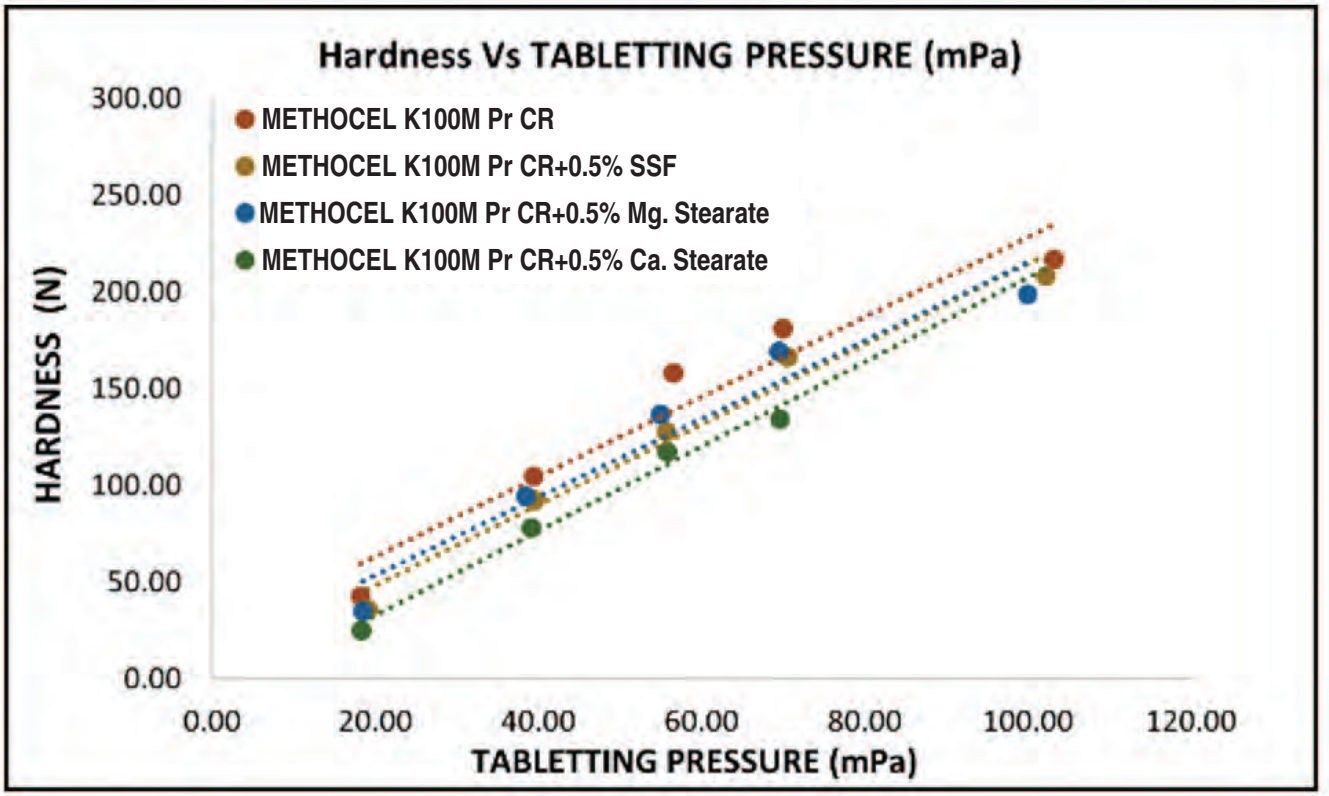
CONCLUSION

These study results show that through polymer chemistry, it is viable to effectively manufacture matrix tablets via a simple direct compression method; and Hypromellose has impressive compatibility at various compression forces. The simulator results show high tablet tensile strength, low tablet friability, and good content uniformity. The excellent flow properties provide processability in direct compression, the preferred industry method. The propranolol HCl release profile from the advanced neat polymer matrix tablets are similar and remained stable following 1 month of storage, under accelerated stability conditions. Therefore, the reproducibility in tablet properties can be higher for direct compression.

The tensile strength of advanced neat polymers was found compatible – along with flow aids such as SSF, fumed silicon dioxide, and magnesium Stearate – without any chipping or capping. Blends with Calcium stearate led to lower compact hardness and capping at higher tableting pressure. However, the hardness of all compacts with other combinations was strong enough to withstand further stress of coating, packaging, and shipping.

Continuous manufacturing is a growing trend and resource-saving technique in pharmaceutical manufacturing. As such, selecting flexible excipients is the best way for formulators to optimize operations and avoid malfunction during the manufacturing process. This study shows co-processed excipients, such as Hypromellose, can help solve many continuous manufacturing issues and allow for any easy transition from batch manu-

FIGURE 4



The hardness of tablets at various tableting pressure for Hypromelloseand compact blend of Magnesium Stearate, Calcium Stearate, and SSF.

facturing. There is shortened development time and up to 60% lowered manufacturing costs through the elimination of the wet granulation process.

Importance of Excipients & Expertise

Formulators whose direct compression tableting operations are faced with particle segregation, poor API content uniformity, and plugging or blocking in the manufacturing process should seek out an excipient that improves powder flow and tablet compatibility, like advanced neat polymers.

To reduce manufacturing steps while producing a quality product, it is also important to choose an excipient that offers functionalities that exceed or build upon traditional excipient blends. The correct excipient can help manufacturers avoid ingredient segregation during the blending process, improve flow, and achieve proper lubrication for one-step mixing. Applying an accelerated formula strategy is one of the best ways to keep savvy formulators ahead of the industry curve.

ACKNOWLEDGEMENT

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REFERENCES

1. Yadav, P., Kumar Sahdev, A. (2018). Physics of tablet with compaction and compression process for novel drug dosage form. International Journal of Advanced Science and Research, 3(4),28-34.
2. Pitt, K.G., Heasley, M.G. (2013). Determination of the tensile strength of elongated tablets. Powder Technology, 238,169-175.

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EXTRACELLULAR VESICLES

Engineering Extracellular Vesicles to Create Next-Generation Therapeutics

By: David Lowe, PhD, Justin Hean, PhD, Dave Carter, PhD, and Antonin de Fougerolles, PhD

INTRODUCTION

Cells from both eukaryotes and bacteria release extracellular vesicles (EVs) as a form of intercellular communication and as a method to regulate biological processes.[1,2] EVs can be broadly defined based on their size and method of cellular biogenesis. Exosomes are small (approximately 30 nm to 150 nm in diameter) extracellular membranous vesicles formed through invagination of the endosomal membrane to form an endosomal multivesicular body (MVB), which fuses with the plasma membrane, releasing the intraluminal vesicles as exosomes.[3] This contrasts with other extracellular vesicles, such as microvesicles (which can range from approximately 100 nm to >1000 nm in diameter), which are released through outward budding of the plasma membrane, or apoptotic bodies, produced during apoptotic cell death.[4] EVs have been shown to be capable of naturally transporting a wide variety of cellular metabolic cargoes, such as proteins, lipids, transcription factors, miRNAs, and mRNA, and it is this natural role of exosomes as "nature's delivery vehicle" that has led to much interest in their potential exploitation for therapeutic use. Most of this therapeutic interest is focussed on exosomes, but as there is still much work to be done in characterising the different classes of EVs from both a biological function, as well as a transcriptomic and proteomic perspective, this review will refer to all types of these bodies as EVs, rather than differentiating between exosomes, microvesicles, or apoptotic bodies, and will focus on emerging engineering approaches to harness the therapeutic potential of EVs.[1]

NON-ENGINEERED EXOSOME THERAPIES

There is now a vast and rapidly growing body of data demonstrating the role of EVs in both physiological and pathological processes.[2,5] EVs released by tumor cells have been associated with increased tumor invasiveness and metastasis.[6,7] EVs have also been shown to contribute to the pathology of atherosclerotic plaques, as well as potentially playing a role in the spread of misfolded neurotoxic proteins, such as prion proteins, amyloid beta, and alpha-synuclein, associated with the pathology of neurodegenerative diseases.[8] In addition, the multiple physiological roles EVs play in healthy cell-to-cell communication has led to much recent interest in their therapeutic application. *In vivo* studies using EVs derived from multiple cell sources have demonstrated therapeutic potential in models of varied diseases, such as cancer, stroke, myocardial ischaemia, as well as vaccines to protect from infections from bacteria and other pathogens. More excitingly, in recent years, human clinical studies have been initiated with EVs derived from mesenchymal stem cells (MSCs) in several therapeutics areas, such as graft-versus-host disease and chronic kidney disease. ExoPharm (Melbourne, Australia) have conducted a successful clinical trial with platelet-derived EVs in healthy volunteers undergoing an experimental skin punch biopsy-induced wound (PLEXOVAL II). The potential use of dendritic cell-derived EVs as vaccines is also under clinical investigation, making use of the presence on these EVs of immunostimulatory proteins and MHC-peptide complexes. The clinical progression of these platelet, MSC, and other cell-derived EV products will necessitate the development of scaled-up manufacturing procedures, particularly in terms of purification and

characterisation methods, as well as analytical techniques to determine product quality and reproducibility. Similarly, the novel nature of EVs as a therapeutic modality will necessitate establishing regulatory paths to the clinic and eventually the marketplace. In order to unlock the full potential of EVs as a therapeutic modality, multiple laboratories are investigating approaches to engineer EVs, through genetic manipulation of EV-associated proteins in the parental cell-line to introduce additional adventitious properties, such as cell or tissue targeting or directed loading of a therapeutic cargo. Additionally, there is much interest in treating EVs as a drug delivery nanoparticle for the loading and delivery of therapeutic molecules, such as chemotherapies and small interfering RNA (siRNA). These exciting approaches will form the bulk of this review.

ENGINEERED EVS AS POTENTIAL THERAPEUTICS

Releasing the inherent potential of EVs as therapeutics and as delivery vehicles for therapeutic cargoes will likely require the optimization of multiple EV characteristics. Depending on the clinical indication and suggested route of administration, some of these might include altering the biodistribution and pharmacokinetics of EVs, as well as maximizing the loading of the therapeutic cargo, either on the surface, or within the lumen of the EV. In order to try to engineer these properties, much research has focussed on identifying and understanding the roles of EV-enriched and associated molecules.[9,10]

EV-ASSOCIATED PROTEINS AS ENGINEERING SCAFFOLDS

The discovery and characterization of the different types of EV rapidly led to proteomic and mechanistic analyses to identify proteins associated with their formation, endogenous cargo loading, secretion, targeting, and uptake.[9] Several key protein families that were found to be enriched in EVs including the tetraspanins, particularly CD9, CD63, and CD81 and members of the ESCRT machinery, such as Alix and TSG-101. Other proteins enriched on or within EVs include lysosome-associated membrane proteins (LAMPs), heat shock proteins (HSPs), major histocompatibility complex (MHC) proteins, adhesion molecules such as intercellular adhesion molecules (ICAMs), integrins and selectins, as well as a wide range of proteins associated with membrane transport and fusion, such as annexins, and GTPases.[11] More recently, the EWI immunoglobulin superfamily member PTGFRN and the MARCKS protein family member BASP1 have been reported to be highly enriched in EVs and to show great versatility as engineering scaffolds.[12] Several of these protein classes, in particular the tetraspanins, and the LAMPs have been successfully used as EV-associated scaffolds for engineering across a wide range of biological contexts (Figure 1).

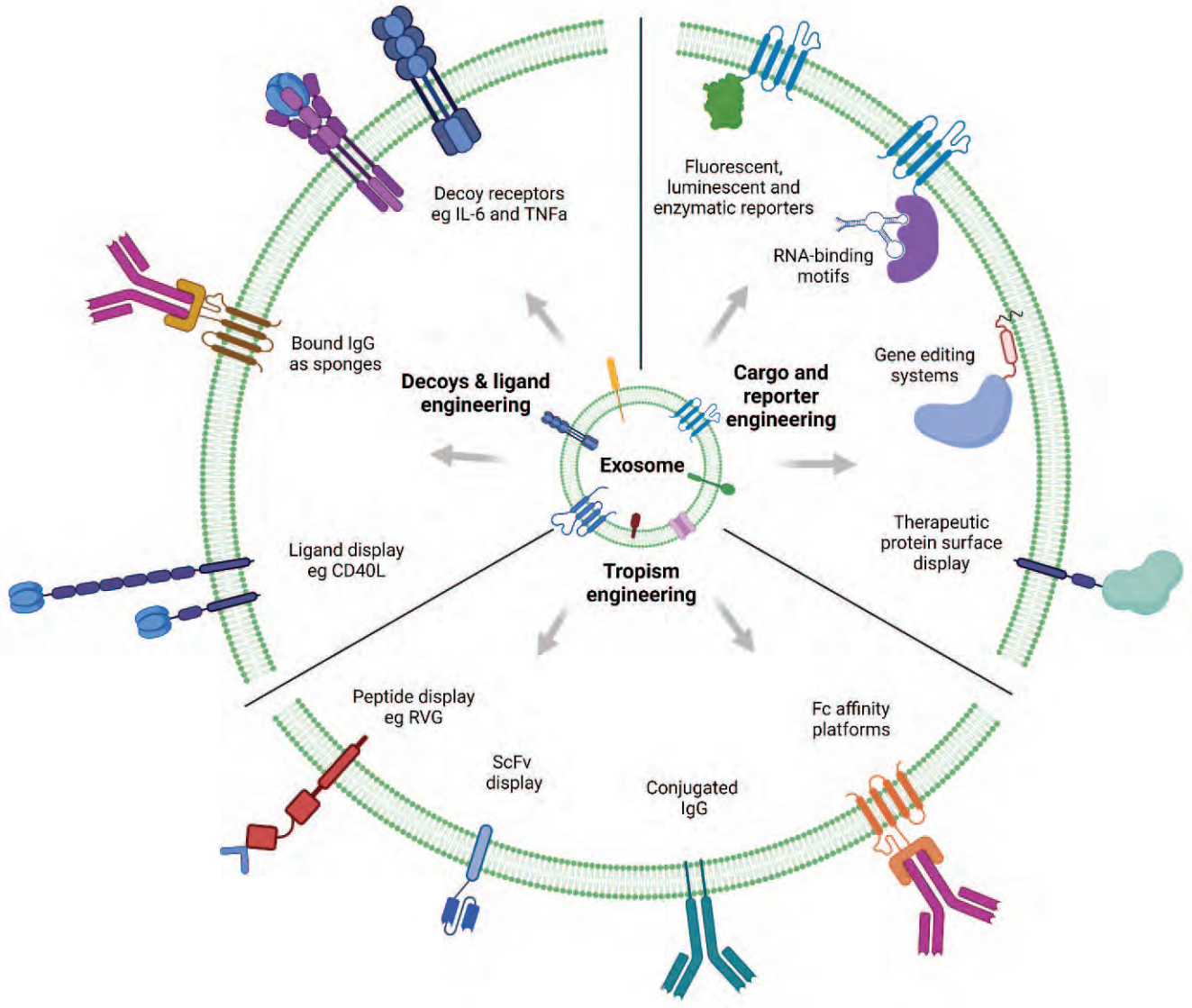
ENGINEERING EVS FOR SPECIFIC TROPISM

EVs typically have rapid pharmacokinetics, with serum half-lives of a few minutes in both rodent and non-human primate (NHP) studies.[13] These studies have shown that systemically delivered EVs rapidly accumulate in the liver and spleen. In order to widen the therapeutic potential of EVs extrahepatically, exosomal scaffold proteins have been engineered with tissue-targeting moieties. An early example of such an approach was the insertion of a peptide derived from the rabies virus glycoprotein (RVG), which has been shown to facilitate drug delivery into the central nervous system into the EV surface associated protein LAMP2B.[14,15] In this study, RVG-LAMP2B-expressing EVs could be shown to functionally deliver siRNA cargo to the CNS, following intravenous injection in mice. Other strategies for optimizing EV transit across the blood-brain barrier include conjugating EVs with anti-CD22.[16] Engineering EVs to display antibodies or antibody fragments is an increasingly powerful way to direct the tropism of the EV to a particular target tissue or cell. Shi et al engineered both anti-CD3 and anti-HER2 single-chain Fv (scFv) fragments fused to the human platelet-derived growth factor receptor (PDGFR) transmembrane domain to generate exosomes that could simultaneously target T cell CD3 and breast cancer expressed HER2 and which exhibited potent *in vitro* and *in vivo* activity.[17] Similarly, Dooley et al successfully fused anti-CD3 antibody fragments to the PTGFRN scaffold protein, resulting in functional engagement with murine T cells.[12]

ENGINEERING EVS FOR ENHANCED PHARMACOKINETICS

As previously noted, systemically administered EVs are rapidly cleared from the serum and accumulate to a significant extent in the liver and spleen within min-

FIGURE 1



EV Engineering Scaffolds & Strategies

utes of dosing. While this type of profile can be desirable in certain clinical settings, engineering approaches that can a) extend the serum half-life in order to facilitate a wider biodistribution, enabling delivery to therapeutic sites of interest, and/or b) prevent EV phagocytosis by macrophages, will likely be required for a successful EV therapeutic in many clinical scenarios. A well-validated approach to extending serum half-life for therapeutic molecules is by binding to serum albumin.[18] Our laboratory has recently incorporated an albumin-binding domain peptide into the extracellular loop of the tetraspanin CD63 and have shown that this extends the serum persistence of EVs following systemic dosing in mice (manuscript in preparation).

Another approach using CD47 involves preventing EV phagocytosis by macrophages. CD47 is an integrin associated transmembrane protein that is the ligand for signal regulatory protein alpha (SIRPα). CD47-SIRPα binding initiates the "don't eat me" signal that inhibits phagocytosis and was shown by Kalluri and colleagues to help EVs avoid rapid degradation by professional phagocytes.[19] Overexpression of such molecules in EVs may represent a strategy to camouflage therapeutic EVs to avoid phagocytosis and thus enhance their pharmacokinetics.[20]

ENGINEERING EVS TO DISPLAY PROTEIN THERAPEUTICS

EVs show great potential as a vehicle for the display of biotherapeutics, such as antibodies and biological receptor proteins, both as potential agonists and as

antagonistic decoy proteins, eg, for proinflammatory cytokines. Gupta et al recently showed that EVs can be engineered to simultaneously express recombinant fusion constructs consisting of domains of EV scaffold proteins fused to the extracellular domains of receptors for the proinflammatory cytokines TNF alpha and IL-6 on their surface.[21] In rodent models of inflammation, these EVs were shown to exhibit potent anti-inflammatory activity greater than that clinically approved biologics targeting the TNF alpha and IL-6 signalling pathways. A similar approach has been taken to express the inflammatory cytokine IL-12 as a fusion with the EV scaffold protein PTGFRN, as a potential anti-cancer treatment.[22] In this study, EVs expressing IL-12 on their surface were shown to potently reduce tumor growth following intratumoral injection. Codiak Biosciences have initiated a Phase 1 clinical trial in cutaneous T cell lymphoma with their exoIL-12 EV product (NCT05156229).

ENGINEERING EVS TO DELIVER PROTEIN CARGOES

In addition to displaying therapeutic or targeting moieties on the EV surface, many researchers have successfully used engineered EVs to deliver intraluminal protein cargoes. Scientists at Evox have developed a proprietary intein-based cleavage system to allow soluble enzymes and proteins to be luminally loaded into exosomes without a need to remain tethered to the exosomal membrane (Evox Therapeutics, manuscript in preparation). Others have demonstrated that genetically fusing target proteins to the EV scaffold protein BASP1 can result in the efficient loading and delivery of cargoes, such as ovalbumin, as well as a bacteriophage-derived RNA-binding protein and the gene editing enzyme Cas9.[12] Codiak Biosciences is using this approach to develop EVs loaded with a cyclic dinucleotide (CDN) stimulator of interferon genes (STING) agonist for clinical development in solid tumors (NCT04592484). A subclass of EVs known as arrestin domain containing protein 1 (ARRDC1)-mediated microvesicles (ARMMs) has been successfully demonstrated to efficiently load (via genetic fusion to the ARRDC1 protein) and deliver a variety of therapeutic cargoes, including p53 and the CRISPR/Cas 9 guide RNA complex.[23,24]

EVS AS A DELIVERY VEHICLE FOR ENDOGENOUSLY LOADED RNA-BASED THERAPIES

EVs typically contain a range of RNA molecules, such as miRNA, lncRNA, and mRNA, and mRNA and their ability to deliver RNA molecules from one cell to another has be long established.[25] Researchers have looked to exploit this natural nucleic acid-loading capability of EVs in order to deliver potentially therapeutic RNA payloads. Liu et al used an approach of directly transfecting siRNA molecules targeting the Mu opioid receptor (MOR), along with an engineered lamp2b construct displaying the RVG peptide into producer cells and demonstrated that the EVs produced by these cells could cross the blood-brain barrier and functionally down-regulate MOR expression.[26] Moreover, they showed that the siRNA was associated with argonaute 2 (AGO2) protein within the EVs, indicating that the proteomic content of the EVs could be potentially exploited to enrich for RNA loading. At around this time, Hung and Leonard took this approach a step further, fusing Lamp2b to the RNA binding bacteriophage coat protein MS2 and engineering the cognate MS2 stem loop sequence into RNA cargoes.[27] Taking this active endogenous-loading approach, which they termed Targeted and Modular EV Loading (TAMEL), they showed that RNA enrichment of up to 40-fold could be observed in EVs derived from cells transfected with this system. An alternative but conceptually similar approach developed by Martin Fussenegger and colleagues used the archaeal ribosomal protein L7Ae, which binds to the C/Dbox RNA structure, fused to the terminus of the tetraspanin CD63, coupled with the insertion of the C/Dbox structure into the 3′ UTR of target mRNA. Using this method, they could produce EVs significantly enriched for the target mRNA, as well as delivery both *in vitro* and *in vivo*.[28] Recent work by Evox Therapeutics using RNA binding proteins loaded into EVs enabled > 100-fold enrichment into exosomes for mRNA containing the cognate recognition motif in its 3′ UTR (Unpublished results).

EVS AS DELIVERY VEHICLE FOR EXOGENOUSLY LOADED RNA-BASED THERAPIES

Electroporation of EVs is a well-established method for exogenously loading them with micro RNAs (miRNAs), siRNAs, and linear DNA. In a seminal study, Matthew Wood and co-workers showed that EVs that had been electroporated with siRNA targeting the Alzheimer disease (AD) target beta-secretase 1 (BACE1) could lead to significant knockdown of BACE1 expression when delivered *in vivo*

in a mouse model of AD.[15] Subsequently, it has been demonstrated that EVs electroporated with siRNA targeting oncogenic mutants of K-ras can potently suppress tumor growth in a mutant Kras-expressing human pancreatic orthotopic tumor mouse model.[29]

A major challenge to using electroporation to load nucleic acid therapies into EVs for clinical development is that of scaling to the large volumes needed to treat patients. Alternative approaches to loading EVs include the use of hydrophobically modified siRNAs.[30] Here, Khorova and colleagues developed cholesterol- conjugated siRNAs targeting Huntingtin mRNA and showed that they could be efficiently incorporated into EVs following incubation without altering EV integrity or size distribution. Moreover, these siRNA-loaded EVs could efficiently silence Huntingtin mRNA and protein when applied to mouse primary cortical neurons. In addition, these siRNA-loaded EVs, unlike the cholesterol-tagged siRNAs alone, were able to efficiently distribute bilaterally across the mouse brain striatum.

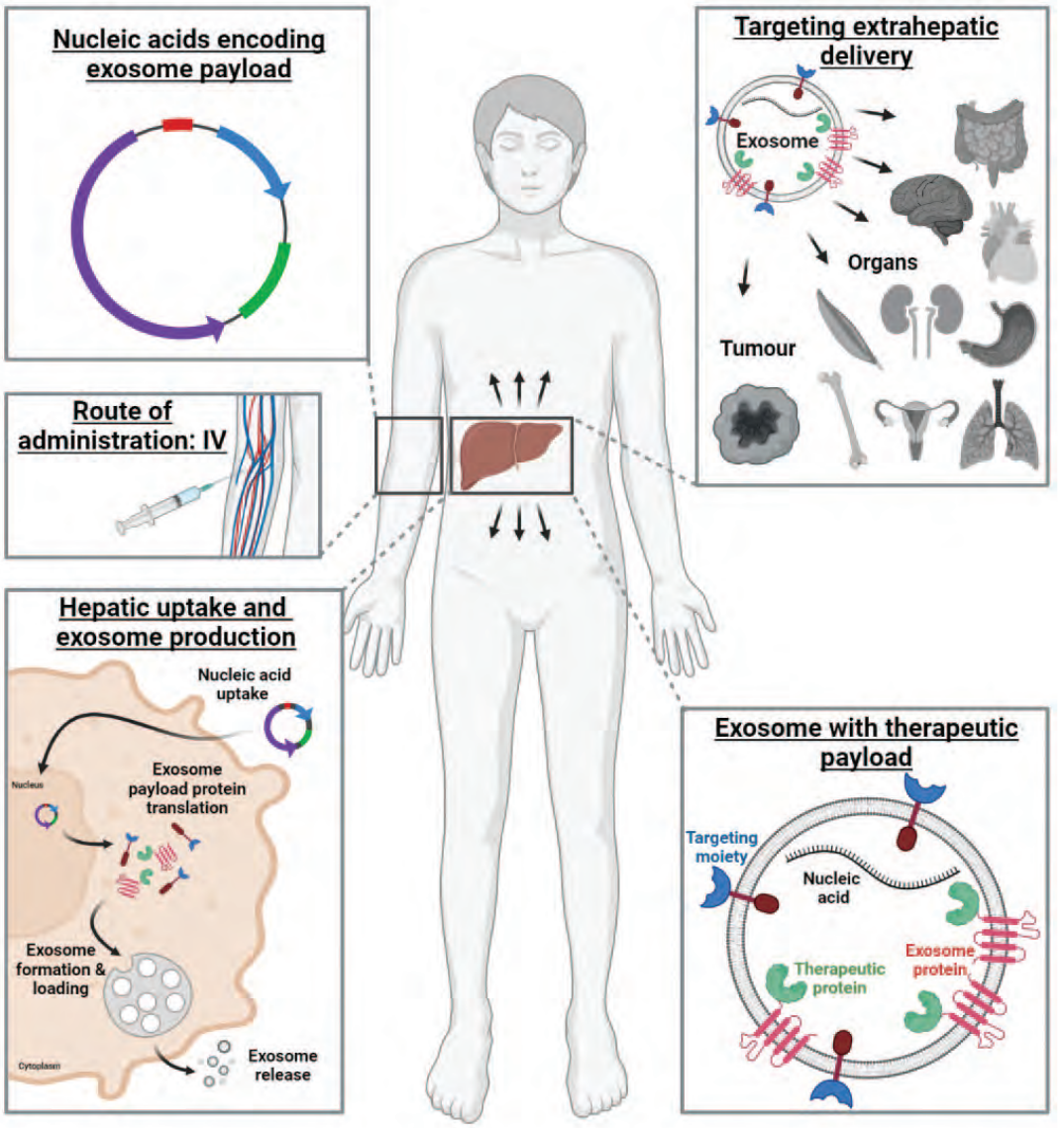
EVS AS A METHOD OF PACKAGING ADENO-ASSOCIATED VIRUS (AAV)

Adeno-associated viruses (AAVs) are a well-established vector for gene therapy, with Luxturna (voretigene neparvovec) approved for the treatment of inherited retinal dystrophy in 2017 and Zolgensma (onasemnogene abeparvovec-xioi) approved for the treatment of spinal muscular atrophy in 2019, as well as over 100 AAV-based therapies under clinical investigation in 2021. AAV therapies still face substantial challenges, notably safety, high dosing requirements, and immunogenicity, with for example, pre-existing neutralizing antibodies against the AAV8 serotype detected in ~30% of screened patients.[31] Casey Maguire and colleagues have demonstrated that AAV associated with EVs (exo-AAV) are able to be isolated through ultracentrifugation and that these exo-AAV show substantial protection from pre-existing antibodies, compared to AAV alone.[32] This approach has been applied to intravitreal injection, where exo-AAV2 was observed to penetrate deeper into the retina than conventional AAV2, efficiently reaching the inner nuclear and outer plexiform.[33] This approach of combining EVs with AAV is potentially a very promising method to address some of the key challenges associated with conventional therapy and may offer a path toward efficient multiple dosing of AAV therapies and the potential for lower therapeutic doses. The requirement for ultracentrifugation to prepare the exo-AAV represents a key challenge to overcome in order to appropriately scale this approach for clinical application, and so development of alternative purification and analytical techniques is likely to be essential. Another area for future development that we and others are exploring involves using EV engineering approaches to actively load AAV into EVs rather than rely solely on passive association of AAV with EVs.

FUTURE PERSPECTIVES

EVs exhibit key properties that make them extremely attractive as therapeutics, particularly their safety profile and potential for low immunogenicity. In order to effectively unlock this potential, some key challenges remain, such as the development of EV product manufacture and characterization methodologies and rapid pharmacokinetics. As discussed in this review, engineering approaches, such as the display of targeting moieties on EV scaffold proteins or the incorporation of "don't-eat-me" signals, such as CD47 into EVs may help to surmount the challenge of rapid clearance and enhance EV biodistribution. One intriguing approach to EV therapy that could address both the manufacturing and pharmacokinetic challenges was recently reported by Fu and colleagues.[34] Here, instead of using purified EVs to deliver siRNA molecules *in vivo*, Fu et al designed DNA vectors encoding the EV-associated protein Lamp2b fused to DNA sequences encoding for siRNAs, all under a CMV promoter. Intravenous delivery of these constructs as plasmids resulted in delivery to the liver, followed by the hepatic production of EVs encoding the siRNAs of interest. Intriguingly, the authors report substantial extrahepatic functional delivery of the siRNA to multiple tissues. By incorporating the RVG peptide into the genetic design, hepatically-generated EVs containing siRNAs designed to knockdown protein tyrosine phosphatase 1b (PTP1b), a potential obesity target associated with leptin and insulin signalling in hypothalamic neurons, were successfully delivered to the brain resulting in PTP1b knockdown and leptin and insulin sensitivity in a mouse model of obesity. This genetic delivery approach to EV production *in vivo* may represent a new paradigm for EV therapeutics, with the potential for a successful marriage of EV delivery of RNAi therapies with more established gene delivery approaches, such as mRNA/LNP or AAV (Figure 2). If successful, this could add substantially to our thinking around the future development of EV-based therapeutics. ◆

FIGURE 2



***In Situ* Expression of EVs Following Gene Delivery**

REFERENCES

1. Y. Couch et al., "A brief history of nearly EV-erything – The rise and rise of extracellular vesicles," Journal of Extracellular Vesicles, vol. 10, no. 14. John Wiley and Sons Inc, Dec. 01, 2021. doi: 10.1002/jev2.12144.
2. M. Yáñez-Mó et al., "Biological properties of extracellular vesicles and their physiological functions," Journal of Extracellular Vesicles, vol. 4, no. 2015. Co-Action Publishing, pp. 1–60, 2015. doi: 10.3402/jev.v4.27066.
3. J. Huotari and A. Helenius, "Endosome maturation," The EMBO Journal, vol. 30, no. 17, pp. 3481–3500, Aug. 2011, doi: 10.1038/emboj.2011.286.
4. A. E. Russell et al., "Biological membranes in EV biogenesis, stability, uptake, and cargo transfer: an ISEV position paper arising from the ISEV membranes and EVs workshop," in Journal of Extracellular Vesicles, Dec. 2019, vol. 8, no. 1. doi: 10.1080/20013078.2019.1684862.
5. A. G. Yates et al., "In sickness and in health: The functional role of extracellular vesicles in physiology and pathology in vivo: Part II: Pathology," Journal of Extracellular Vesicles, vol. 11, no. 1. John Wiley and Sons Inc, Jan. 01, 2022. doi: 10.1002/jev2.12190.
6. K. Meehan and L. J. Vella, "The contribution of tumour-derived exosomes to the hallmarks of cancer.," Crit Rev Clin Lab Sci, vol. 53, no. 2, pp. 121–31, 2016, doi: 10.3109/10408363.2015.1092496.
7. G. Chen et al., "Exosomal PD-L1 contributes to immunosuppression and is associated with anti-PD-1 response," Nature, vol. 560, no. 7718, pp. 382–386, Aug. 2018, doi: 10.1038/s41586-018-0392-8.
8. B. B. Guo, S. A. Bellingham, and A. F. Hill, "Stimulating the Release of Exosomes Increases the Intercellular Transfer of Prions.," J Biol Chem, vol. 291, no. 10, pp. 5128–37, Mar. 2016, doi: 10.1074/jbc.M115.684258.
9. S. Gurung, D. Perocheau, L. Touramanidou, and J. Baruteau, "The exosome journey: from biogenesis to uptake and intracellular signalling," Cell Communication and Signaling, vol. 19, no. 1. BioMed Central Ltd, Dec. 01, 2021. doi: 10.1186/s12964-021-00730-1.
10. Z. Andreu and M. Yáñez-Mó, "Tetraspanins in extracellular vesicle formation and function," Frontiers in Immunology, vol. 5, no. SEP, 2014, doi: 10.3389/fimmu.2014.00442.
11. D.-K. Kim, J. Lee, R. J. Simpson, J. Lötvall, and Y. S. Gho, "EVpedia: A community web resource for prokaryotic and eukaryotic extracellular vesicles research.," Semin Cell Dev Biol, vol. 40, pp. 4–7, Apr. 2015, doi: 10.1016/j.semcdb.2015.02.005.
12. K. Dooley et al., "A versatile platform for generating engineered extracellular vesicles with defined therapeutic properties," Molecular Therapy, vol. 29, no. 5, pp. 1729–1743, May 2021, doi: 10.1016/j.ymthe.2021.01.020.
13. M. Morishita, Y. Takahashi, M. Nishikawa, and Y. Takakura, "Pharmacokinetics of Exosomes-An Important Factor for Elucidating the Biological Roles of Exosomes and for the Development of Exosome-Based Therapeutics.," J Pharm Sci, vol. 106, no. 9, pp. 2265–2269, 2017, doi: 10.1016/j.xphs.2017.02.030.
14. R. Huey, S. Hawthorne, and P. McCarron, "The potential use of rabies virus glycoprotein-derived peptides to facilitate drug delivery into the central nervous system: a mini review.," J Drug Target, vol. 25, no. 5, pp. 379–385, Jun. 2017, doi: 10.1080/1061186X.2016.1223676.
15. L. Alvarez-Erviti, Y. Seow, H. Yin, C. Betts, S. Lakhal, and M. J. A. Wood, "Delivery of siRNA to the mouse brain by systemic injection of targeted exosomes," Nature Biotechnology, vol. 29, no. 4, pp. 341–345, Apr. 2011, doi: 10.1038/nbt.1807.
16. X. Liu et al., "Overcoming the blood-brain barrier by using a multistage exosome delivery system to inhibit central nervous system lymphoma.," Nanomedicine, vol. 41, p. 102523, 2022, doi: 10.1016/j.nano.2022.102523.
17. X. Shi et al., "Genetically Engineered Cell-Derived Nanoparticles for Targeted Breast Cancer Immunotherapy," Molecular Therapy, vol. 28, no. 2, pp. 536–547, Feb. 2020, doi: 10.1016/j.ymthe.2019.11.020.
18. D. Pilati and K. A. Howard, "Albumin-based drug designs for pharmacokinetic modulation.," Expert Opin Drug Metab Toxicol, vol. 16, no. 9, pp. 783–795, Sep. 2020, doi: 10.1080/17425255.2020.1801633.

19. S. Kamerkar et al., "Exosomes facilitate therapeutic targeting of oncogenic KRAS in pancreatic cancer," Nature, vol. 546, no. 7659, pp. 498–503, Jun. 2017, doi: 10.1038/nature22341.
20. N. Parada, A. Romero-Trujillo, N. Georges, and F. Alcayaga-Miranda, "Camouflage strategies for therapeutic exosomes evasion from phagocytosis," Journal of Advanced Research, vol. 31. Elsevier B.V., pp. 61–74, Jul. 01, 2021. doi: 10.1016/j.jare.2021.01.001.
21. D. Gupta et al., "Amelioration of systemic inflammation via the display of two different decoy protein receptors on extracellular vesicles.," Nat Biomed Eng, vol. 5, no. 9, pp. 1084–1098, 2021, doi: 10.1038/s41551-021-00792-z.
22. N. D. Lewis et al., "Exosome surface display of IL12 results in tumor-retained pharmacology with superior potency and limited systemic exposure compared with recombinant IL12," Molecular Cancer Therapeutics, vol. 20, no. 3, pp. 523–534, Mar. 2021, doi: 10.1158/1535-7163.MCT-20-0484.
23. Q. Wang, J. Yu, T. Kadungure, J. Beyene, H. Zhang, and Q. Lu, "ARMMs as a versatile platform for intracellular delivery of macromolecules," Nature Communications, vol. 9, no. 1, Dec. 2018, doi: 10.1038/s41467-018-03390-x.
24. H. Choi et al., "Exosome-based delivery of super-repressor IκBα relieves sepsis-associated organ damage and mortality.," Sci Adv, vol. 6, no. 15, p. eaaz6980, 2020, doi: 10.1126/sciadv.aaz6980.
25. L. Cheng and A. F. Hill, "Therapeutically harnessing extracellular vesicles," Nature Reviews Drug Discovery, Mar. 2022, doi: 10.1038/s41573-022-00410-w.
26. Y. Liu et al., "Targeted exosome-mediated delivery of opioid receptor Mu siRNA for the treatment of morphine relapse.," Sci Rep, vol. 5, p. 17543, Dec. 2015, doi: 10.1038/srep17543.
27. M. E. Hung and J. N. Leonard, "A platform for actively loading cargo RNA to elucidate limiting steps in EV-mediated delivery.," J Extracell Vesicles, vol. 5, p. 31027, 2016, doi: 10.3402/jev.v5.31027.
28. R. Kojima et al., "Designer exosomes produced by implanted cells intracerebrally deliver therapeutic cargo for Parkinson's disease treatment," Nature Communications, vol. 9, no. 1, Dec. 2018, doi: 10.1038/s41467-018-03733-8.
29. M. Mendt et al., "Generation and testing of clinical-grade exosomes for pancreatic cancer," JCI Insight, vol. 3, no. 8, Apr. 2018, doi: 10.1172/jci.insight.99263.
30. M. C. Didiot et al., "Exosome-mediated delivery of hydrophobically modified siRNA for huntingtin mRNA silencing," Molecular Therapy, vol. 24, no. 10, pp. 1836–1847, Oct. 2016, doi: 10.1038/mt.2016.126.
31. S. J. Aronson et al., "Prevalence and Relevance of Pre-Existing Anti-Adeno-Associated Virus Immunity in the Context of Gene Therapy for Crigler-Najjar Syndrome.," Hum Gene Ther, vol. 30, no. 10, pp. 1297–1305, 2019, doi: 10.1089/hum.2019.143.
32. B. György, Z. Fitzpatrick, M. H. W. Crommentuijn, D. Mu, and C. A. Maguire, "Naturally enveloped AAV vectors for shielding neutralizing antibodies and robust gene delivery invivo," Biomaterials, vol. 35, no. 26, pp. 7598–7609, 2014, doi: 10.1016/j.biomaterials.2014.05.032.
33. S. J. Wassmer, L. S. Carvalho, B. György, L. H. Vandenberghe, and C. A. Maguire, "Exosome-associated AAV2 vector mediates robust gene delivery into the murine retina upon intravitreal injection.," Sci Rep, vol. 7, p. 45329, 2017, doi: 10.1038/srep45329.
34. Z. Fu et al., "In vivo self-assembled small RNAs as a new generation of RNAi therapeutics," Cell Research, vol. 31, no. 6, pp. 631–648, Jun. 2021, doi: 10.1038/s41422-021-00491-z.

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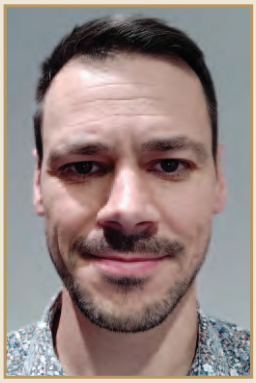
BIOGRAPHIES

Dr. David Lowe is Vice President, Research, at Evox Therapeutics, and has more than 20 years of biotech and large pharma R&D experience in advancing protein and antibody-based therapeutics as well as exploring novel therapeutic modalities, such as gene therapy, mRNA therapeutics, and exosomes. Prior to his joining Evox, he spent more than 12 years at AstraZeneca, most recently as Senior Director in charge of Biologics Engineering.



Dr. Justin Hean has spent more than a decade within the exosomal field, having spent half that time developing with Evox Therapeutics, making him one of Evox's longest-serving staff members. He has particular interest in the alteration of exosomes and their production for therapeutic benefit. Currently, he leads a team exploiting facets of exosome engineering, including luminal loading of beneficial payload and surface decoration of functional ligands.

Dr. Dave Carter has more than 15 years of leading multidisciplinary research projects in the exosome field. As a Professor in Biomedical Science at Oxford Brookes University, he secured over £1m in grant funding, published more than 50 papers, and served as the first President of the UK Society for Extracellular Vesicles, before joining Evox in 2021 as Research Director in Exosome Engineering.

Dr. Antonin de Fougerolles is Chief Executive Officer of Evox Therapeutics, and has more than 20 years of biotech R&D experience in building out drug pipelines. He has played a key role in developing and successfully advancing three new drug modalities toward the market and in helping build several multi-billion dollar companies from the start-up stage, including Moderna, Alnylam, and Ablynx.

CLINICAL TRIALS

Quality Matters in an Evolving Clinical Trial Landscape

By: John Buchan

INTRODUCTION

The strive to deliver the very best outcomes sits at the heart of clinical research. Arguably the mechanism for delivering that "perfect" outcome rests squarely on the shoulder of a single key principle – quality. Quality in all areas from study design to data collection to successful publication and many more.

The concept of quality encompasses a vast array of perspectives gained from the evolution of trends in the development of quality management practices. Good Clinical Practice (GCP) is regarded as the ethical and scientific quality standard for conducting a trial and applies to all steps in the process that bring a trial to a successful conclusion. GCP's role is to ensure that the clinical trial data and reported results are credible and accurate and that the rights, integrity, and confidentiality of the trial subjects are protected.

As clinical research becomes more and more complex, small nuances potentially have a big impact on outcomes. Globalization, outsourcing, and increasing regulatory demands are all affecting clinical trials and their quality. Artificial Intelligence (AI) and machine learning (ML) are contributing new ways of discovering and acting on data management in clinical trials, including discovering any anomalies in the data.

Concurrently, wearables and mobile technologies along with cloud technology and related platforms enable the collection of frequent, specific, and multidimensional data but can pose new challenges to collecting and distributing quality clinical trial information. Clinical trial participants are often using these devices in a remote way that requires diligent work on the part of the clinician to ensure data is properly classified and disseminated throughout the appropriate channels. Social media is a rapidly increasing data source for clinical research, but the quality and ultimate validity of the information reported continues to be concern for many.

Investigator sites and Institutional Review Boards (IRBs) have been under increasing scrutiny by the US Food and Drug Administration, the European Medicines Agency (EMA), and the UK's Medicine and Healthcare Products Regulatory agency (MHRA) when it comes to quality. To meet the regulatory expectations, sponsors and Clinical Research Organizations (CRO) need to improve quality by developing systems with specific standards for each clinical trial process.

This article will review best practices for achieving quality by addressing challenges focused on the all-important but growing complexity of managing the distribution of critical safety documents and the processing of Individual Case Study Reports (ICSRs) and aggregate reports to sites, Ethic Committees (ECs), IRBs, and others in the reporting chain.

Quality systems have many touch points including personnel roles and responsibilities, training, policies and procedures, quality assurance and auditing, document management, record retention, and reporting and corrective and preventive action. With an objective to improve quality, newer inspection approaches, such as risk-based inspections, surveillance inspections, real-time oversight, and audit of sponsor quality systems, have become a focal point.

As one example, the FDA has partnered with Duke University to implement the Clinical Trials Transformation Initiative in order to conduct research projects on design principles, data quality and quantity including monitoring, study start-up, and adverse event reporting. This public-private partnership is intended to drive adoption of practices that will increase the quality and efficiency of clinical trials.

MINIMIZING THE POTENTIAL FOR HUMAN ERROR

Rejection of clinical trial data after an inspection is ineffective and even worse, wasteful in time and cost. A better approach to avoid post-inspection waste is to change the process from focusing on inspection-based quality improvement to focusing on proactively determining and finally deploying specific, automated, and documented processes for quality management. When these business processes have been defined and potentially redesigned, the often error-prone human element is greatly reduced.

For example, when key processes for safety document distribution require multiple steps that involve constant manual intervention, often using systems and tools that were not designed for that purpose, undetected small errors can combine into large-scale problems. An automated process, designed for purpose, provides structure and a degree of rigidity, which means that the documents are getting to the right people at the right time, every time. Monitoring with a central dashboard means the process is transparent and controlled.

Globalization of clinical trials has put added pressure on quality measures. When, for example, six sites with thousands of participants are running in multiple geographic areas and time zones, it is almost impossible for manual intervention processes to ensure the vigilance necessary to meet rigid – and varying - regulations for delivering error-free and on-time safety information.

QUALITY IN ROLES & RESPONSIBILITIES

Quality also permeates the development of specific roles and responsibilities of the teams managing and monitoring

the trial sites – and there can be various people involved - including but not limited to the principal investigator (PI), Study Manager, Site Mangers, Clinical Research Associates (CRAs), et al.

Again, globalization causes challenges in maintaining clear oversight of processes when working with a variety of people often with different skill levels or experience in clinical trial management. The methods and degrees of monitoring vary from one clinical trial to another depending on the degree of risk involved and the size and complexity of the trial. While sponsors and CROs want to make sure the teams in charge are well-qualified, it's not always possible to recruit the levels of expertise needed to ensure the most clear and transparent outcomes. Some team participants may be contract workers/freelancers and Site Managers may be simultaneously working on several different trials. This can present the Study Manager with that uncomfortable question "how confident are you in the validity of data from ALL your sites?" Let's not forget that it is the study manager who is ultimately responsible for safety document distribution. Manual assembly of this information is labor intensive, costly, offers opportunity for errors, and often lacks documented audit trails.

Automating the safety document distribution process clearly delivers a significant advantage. Utilizing a central "hub" into which documentation is delivered from each site can provide a clear and transparent advantage. Such automated systems to date have provided a portal into which documents are entered which, while a significant step forward, creates the issue of access and password retention for sites. However, the latest applications have solved this issue and allow secured, validated, and auditable access for all authorized users without the need for passwords. The result is an easy-to-use platform for all trial sites. Depending on different roles identified at each site, there is tiered access to appropriate information. For example, a local investigator may only have access to local sites while Study Managers have access to all sites, no matter the geographic area. This empowers study team members and simplifies access to a real-time overview, significantly reducing the workload across the team and enhancing collaborative communication. For example, in a recent case, a trial team that applied the automated interactive hub approach, in just 1 month, moved from struggling to deliver 20 safety documents a day with its manual system to easily delivering more than 50 documents daily via automation of the process.

QUALITY OF DELIVERY & OVERSIGHT

Depending on their local infrastructure and regulations, sites expect to be able to receive information according to their preferred method, and the information must be blinded or unblinded depending on specific regulations. This means recipients expect to have courier deliveries, email with attachment, email with secure link, even fax. Any automated systems that are supporting recipients must have this flexibility, not only to ensure strong adoption, but also to deliver a unified view of compliance for the sponsor. Regardless of the distribution method, the transparent oversight of the activity must remain.

With a single view, on a dashboard,

the hub approach illuminates all the distinct actions and rates of progress behind each specific process, which means faster and more-informed decision-making and certainty of outcome. For example, country rules that drive the safety document distribution are audit-proof. That means the people on the team responsible are able to see to whom a document was sent, why it was sent on a specific date, and confirmation of receipt. Supporting this effort are automated compliance reports that can identify anomalies at a site, ie, if perhaps more training is needed to ensure better adherence to policies and procedures.

QUALITY IN EXECUTION

Seeking an automated approach can often seem daunting. Will a new system fit easily into the existing infrastructure, will it easily connect to an existing safety database and CTMS, and will it be intuitive enough not to cause interruptions in human adoption? These are all significant questions. Perhaps the simplest answer is that full automation leads to a more streamlined process that naturally enhances the availability of critical information and provides flexibility and clarity in reporting. It also reduces manual efforts, human errors, and operational costs associated with audit trails and compliance documentation. Where solutions have been successfully implemented, they have seen significant reduction in cost and resource requirements and seen much improved compliance from sites.

In short, focusing on quality in all aspects of a clinical trial is the foundation for delivering valid and compliant outcomes. With a simple, easily implemented, automated, interactive, and central database, a commitment to maintaining data integrity and participant safety through quality guidelines provides a systematic approach to continuous process improvement. ◆

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BIOGRAPHY

John Buchan is a Life Science Technology Specialist for pharmasol. He has spent his career in Life Sciences and Life Science technology, the latter specializing in Pharmacovigilance. Having worked in Sales & Marketing roles in major Pharma companies, he moved into working with organizations supplying technology, software, and services for Life Science and Healthcare organizations across Europe and North America. He is a passionate advocate of utilizing the best of technology to solve the challenges the pharmaceutical industry faces. He is based in the southern United Kingdom.

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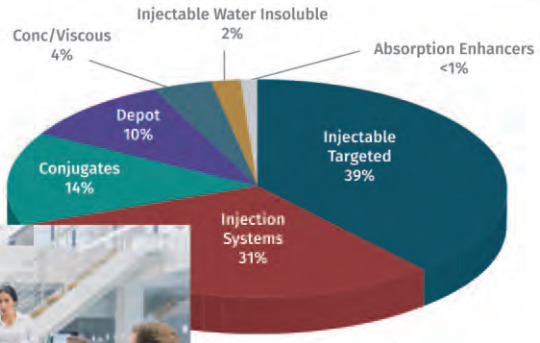
Evaluate New and Promising Technologies



Injectable Drug Delivery Technologies

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INNOVATION WITHOUT CHANGE

Credence MedSystems: Implementing a Flexible Manufacturing Line to Deliver Innovation in Drug Delivery to the Pharmaceutical Industry

The demands on injectable drug delivery systems are increasing. Baseline requirements continue to include successful delivery of the dose, ease-of-use, and safety, but as the complexity of molecules increases and focus areas of pharmaceutical manufacturers expand, these needs are being complemented by factors related to sustainability, cost of ownership, and platform flexibility. Credence MedSystems has developed a platform of drug delivery systems that addresses an array of unmet needs and is now implementing a manufacturing capability with the flexibility to produce numerous configurations of its flagship products. *Drug Development & Delivery* recently interviewed Jeffrey Tillack, Chief Operating Officer at Credence MedSystems, to discuss the challenges being addressed by Credence's innovative technology and the role Credence's new Flex Line will play in the company's scaling strategy.

Q: Can you share a bit about Credence and the path the company is on?

A: Thanks for asking. Credence is a privately funded company that was started in 2013, so we are coming up on our tenth year. The company is located in the heart of Silicon Valley and is dedicated to bringing that innovative spirit to the pharmaceutical industry. We started with a blank sheet of paper and the fundamental idea of incorporating our technology with existing primary package components to create value-added delivery

systems that solve challenges in injectable drug delivery. We call this *Innovation Without Change* because we enable pharma to implement our innovative solutions while leveraging existing supply chain preferences and established processes.

Last year, we announced we had secured almost $40 million in funding, which included strategic investments into Credence by Novartis Pharma and Molex Ventures. That funding and those collaborations have enabled us to accelerate the trajectory of the company as we are now implementing the next phase of our manufacturing scaling plan, which we call the Flex Clinical Line.

Q: You talk about solving challenges in injectable drug delivery. What challenges and unsolved problems is Credence addressing with your technology?

A: Credence's flagship products include the Credence Companion Safety Syringe System and the Credence Dual Chamber Syringe System. These products address challenges across the range of constituents from the user to the pharmaceutical manufacturer.

For the user, who may be an HCP or a self-injector, it's about making administration of the dose easier and safer. For example, the Companion Syringe System turns an existing syringe barrel into a delivery system with end-of-dose cues and integrated, passive needle safety. Numerous user studies have demonstrated preference for Companion over alternative approaches, driven in part by the automatic needle retraction at the end of the injection and the accompanying audible and tactile click. That click communicates that the dose is complete, the needle is protected, and the syringe is prevented from reuse.

The Dual Chamber Syringe System enables complex drug products, which require separation of drug and/or diluent components during storage, to be administered in a fashion that matches as closely as possible that of a standard prefilled syringe. The Dual Chamber platform can be used for reconstitution or for sequential injection of two liquids. In the case of reconstitution, the user simply pushes on the plunger rod to transfer the diluent from the rear chamber so that it can mix with the lyo cake, powder, or liquid in the front chamber. Then, once the solution is mixed, the user can inject. For the sequential delivery of two different liquids, the user simply pushes on the plunger rod. Two liquids that were stored separately are injected one after the other with a continuous push. In either configuration, the completion of the injection activates the same safety mechanism seen in the Companion system.

Shifting focus to the pharmaceutical manufacturer, these systems enable pharma to provide their end-users with an improved, easy, and safe way to deliver their critical medicines, thus driving differentiation for their products in a crowded market. Beyond this, they address other significant challenges and corporate objectives. By integrating the Companion safety mechanism and the Dual Chamber mixing mechanism into the syringe barrel, operational efficiency is enhanced. Secondary manufacturing processes are eliminated, along with the associated scrap and additional capital expenditures that result from those additional processes. Pharma's sustainability efforts are supported by the reduced environmental footprint of these systems. For example, when compared to an alternative add-on safety device, Companion reduces the plastic consumed by 62%, reduces the weight of added components by 58%, and reduces the footprint by 67%. These operational and sustainability advantages lead to total cost of ownership advantages.

In addition, Dual Chamber replaces the traditional kits composed of multiple vials, syringes, needles, adapters, and other ancillary components, which require multiple complex use steps. The benefits of the Dual Chamber include increased ease and speed of preparation and administration, reduced risk of contamination and dosing error, reduced wasted drug from vial overfill requirements, and less dependance on healthcare professionals for administration, storage, and disposal. All of these advantages also contribute to a better, safer user experience and a reduction in total costs per dose administered.

For both pharma manufacturers and the syringe manufacturers, these systems provide broad platform flexibility to address the needs of different applications and user populations. A wide array of needle gauge/length and syringe barrel options are possible. For instance, Credence is working on Dual Chamber applications in syringe barrels ranging from 1 mL long to 20 mL, in both glass and polymer barrels, either with a preattached retracting needle or with a needleless luer lock front end. Companion applications exist in the common 1 mL long and 2.25 mL sizes as well as in new formats such as a 3 mL pre-attached needle configuration. Credence technology allows our pharma customers and syringe barrel manufacturers to get more out of the already existing portfolio of offerings.

Q: What are Credence's plans for scaling the manufacturing of these delivery systems, and where is Credence in that process?

A: Over the past years as these systems have been in development, Credence has supplied our Pharma customers from our pilot manufacturing capability in California. This has enabled us to support development activities such as technical evaluations, pilot stability studies, human factors evaluations, etc. We are in the midst of implementing the next step in scaling, which is the Flex Clinical Line to significantly increase our capacity off of a validated GMP line. At the time of this interview, that line is going through FAT (factory acceptance test) at the equipment manufacturer, and it will then be shipped to its final destination. Soon after, Credence will initiate the commercial production line, which will produce at a capacity of about 50 million units per year, allowing us to meet the large demand at market competitive price points.

Q: The Flex Clinical Line is a big step for Credence. Can you tell us about its capabilities and how it will allow you to meet your customers' needs?

A: It is a big and important step in the company's trajectory. As I mentioned, the investment round and great strategic collaborators have enabled us to take this step. The line was built by Mikron in their Denver facility on their Minicells platform. It will be run by our contract manufacturing partner Phillips-Medisize in their Letterkenny, Ireland, facility. Phillips-Medisize is a Molex company and long-term collaborator with Credence. The line will be up and running in Q4 of this year. It will run both our Companion and Dual Chamber product lines with an annual capacity of approximately 500,000 units per year, depending on product mix.

As the name implies, this has been designed to be highly flexible to produce a broad array of the configurations enabled by our technology. In fact, the line will produce over 100 variations of Companion and Dual Chamber, with a range of needle gauges, needle lengths, and barrel sizes. The line will be in a clean room and, once the appropriate validations are complete, will be able to supply for-human-use product. With this flexibility and capability, the Flex Clinical Line is the perfect fit for what Credence and our customers need today; we will be able to supply meaningful volumes across a wide array of products to support our customers in development stages from technical evaluation and human factors…to stability and validation…to supply for clinical use in Phase 2 and Phase 3 programs.

Q: Why did Credence decide to partner with a Contract Manufacturer rather than build your own capability in house?

A: This is an important question. Certainly, we could have done the latter; our team has experience building greenfield manufacturing. But partnering with a CMO really made more sense for Credence and our business model. Fundamentally, the expertise exists to manufacture our products, and therefore, building from the ground up did not make financial sense. But just as important, we are doing everything we can to facilitate Pharma's implementation of our technology. This applies to our design philosophy of integrating with industry standard syringe barrels and components, and it applies to our manufacturing philosophy. By working with an established global partner like Phillips-Medisize, Credence is able to mitigate risk in the supply chain for our Pharma customers. It gets back to the concept of *Innovation Without Change*. Delivering innovative technology that addresses unmet challenges in drug delivery, and doing so in an implementable way that leverages existing products and processes, is what sets Credence MedSystems apart. ◆

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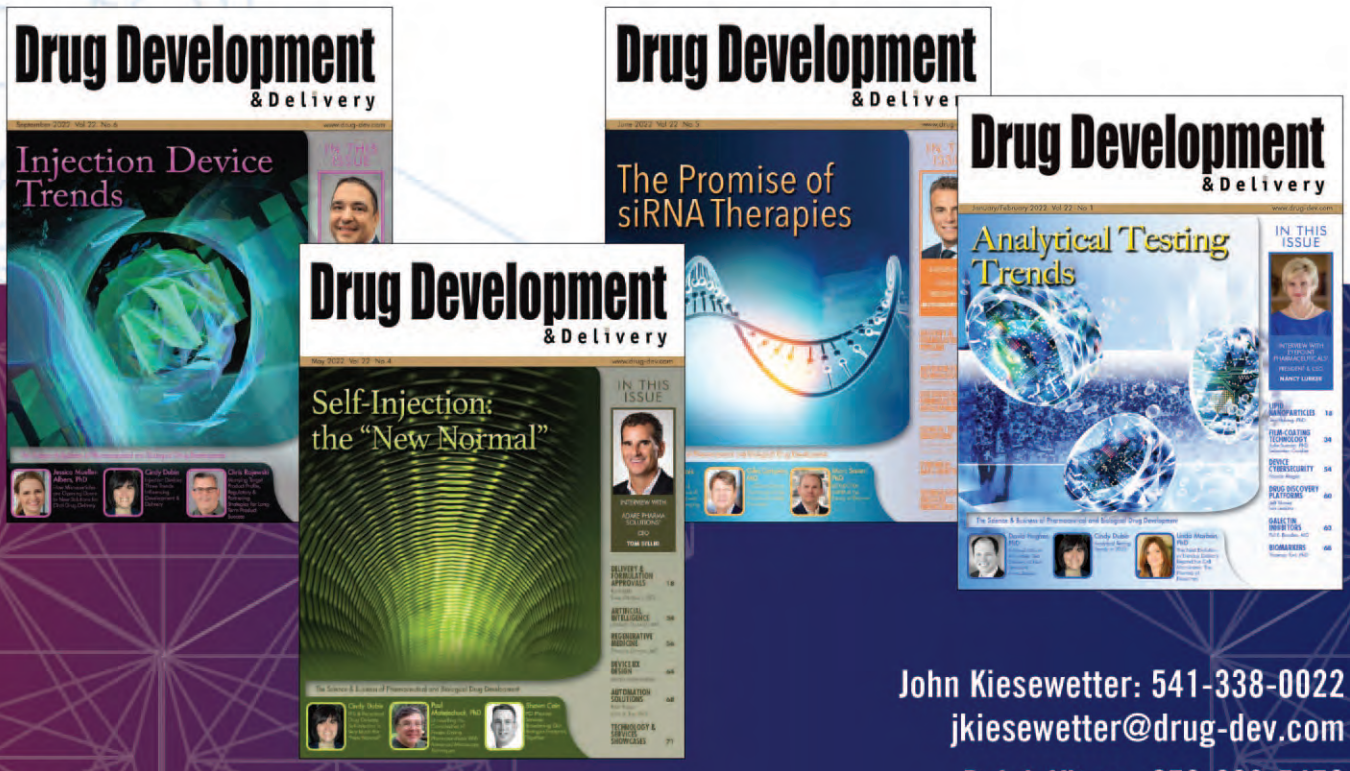

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DRUG DISCOVERY

Getting the Most From a DNA-Encoded Library Screen

By: Matthew A. Clark, PhD

A POWERFUL TOOL FOR LEAD DISCOVERY

DNA-encoded library (DEL) technology has emerged in the past 10 years as a powerful and innovative approach to pharmaceutical lead discovery.[1] By harnessing the power of molecular biology, DEL technology allows the screening of chemical libraries with unprecedented size and diversity. In addition, because the libraries are screened as mixtures, the entire screening experiment can be conducted in a volume of a few microliters. This allows screens to be multiplexed across various parameters to produce uniquely informative output data.

Most large pharmaceutical companies now access a DEL platform, either through partnering or an internal capability or a hybrid of the two. Smaller biotech companies are increasingly interested in accessing DEL to help build their pipelines. Despite this high level of interest, there remains variable understanding of how to maximize the potential of a DEL screen. The following will share how we at X-Chem think about DEL screening and how our partners get the most from this powerful technology when working with our platform.

WHAT IS DEL?

DEL technology is rooted in the challenge of combinatorial chemical synthesis. Starting in the 1990s, chemists found that large numbers of compounds could be prepared through a procedure known as split-and-pool synthesis, where all possible combinations of individual reactants are used to generate large numbers of different products. While large libraries could be conveniently created, identifying the active library members was a challenge. Compounds were often attached to beads, where most analytical methods cannot operate.

These challenges were addressed through the concept of encoding. In an encoded library, an easily analyzable chemical system is employed as an identifier for the library compounds of interest. Many encoding schemes were developed, notably the Still GC tagging system, later employed by Pharmacopeia.[2] The idea of using DNA as the encoding element was first proposed in 1992, and its advantages as an information storing chemical system were immediately apparent.[3]

It took another 15 years, however, for DNA-encoding to really take hold. The key advance was the recognition that one could discard the bead and synthesize the libraries as mixtures in solution. Borrowing from molecular evolution techniques, the resulting encoded mixtures could be enriched for binders by affinity-mediated selection procedures, and the identities of the ligands decoded through DNA sequencing of the retained fraction.

PROTEIN REAGENTS ARE DRIVERS OF SUCCESSFUL DEL SCREENING

"Garbage in, garbage out" is a truism that can be applied to numerous processes and experiments in science and beyond. A DEL selection experiment is no different. The discovery of ligands from numerically large encoded libraries depends on the

physical segregation of the binders from the bulk library. This separation is achieved by exposing the library to the protein of interest and removing the unbound fraction by washing. Obviously, the quality of the protein reagent will be a primary factor in the quality of the screening output.

In functional screening paradigms, such as HTS, the primary quality metric is the reproducibility and signal-to-noise ratio of the functional assay, often expressed as the Z′.[4] By optimizing assay conditions and choosing the appropriate reagents, high Z′ values can be achieved even with relatively crude protein samples. This stands in contrast to biophysical screening techniques, such as crystallography, SPR, ASMS, or DEL, in which the primary quality metrics are related to the purity, aggregation state, and fraction of the protein sample that is in the biologically relevant conformation.

At X-Chem, we subject protein reagents to a rigorous qualification process that includes solution-phase techniques, including dynamic light-scattering (DLS), size-exclusion chromatography (SEC), and differential scanning fluorimetry (DSF), as well as capture assessment and the assessment of the maintenance of appropriate conformation and accessibility in the immobilized state. We sometimes observe that protein samples that are amenable to functional assay development do not meet our standards for DEL screening.

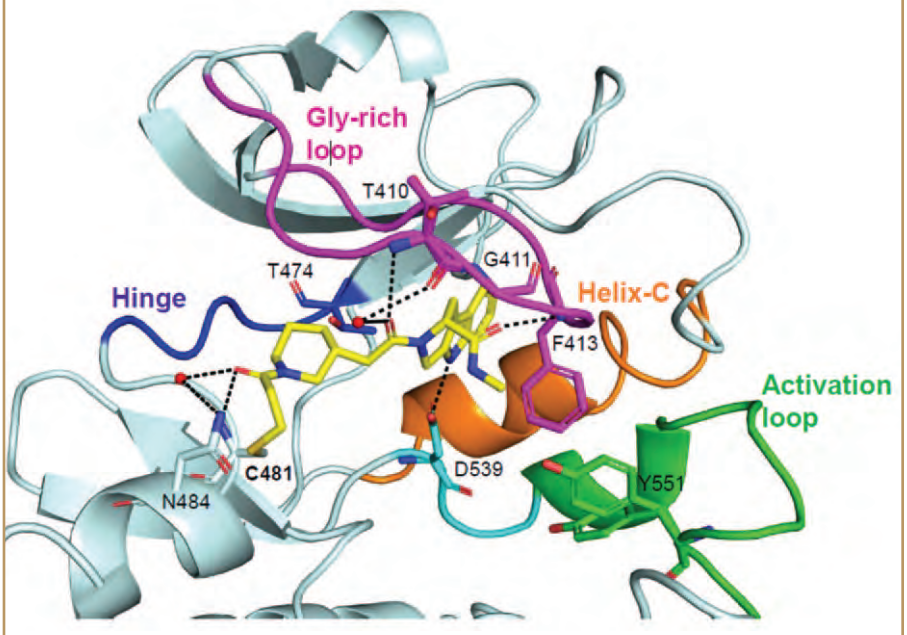
For researchers considering a DEL screen for pharmaceutical hit generation, we would make the following recommendations:

1. If you do not have an internal protein production capability, partner with a premium provider. Companies that provide access to structural biology capability often have expertise in generating high-quality protein. We have found that providers, such as Proteros, can offer a differentiated capability in delivering high-quality protein (as well as biophysical assays and structures). X-Chem and Proteros have a rich history of pairing high-quality reagents with DEL screening.

2. If you do have an internal capability, be sure to set stringent criteria for the reagents you will produce for DEL screening. Reagents generated for X-ray crystallography often meet our quality requirements.

3. Consider exploring alternative selection modalities that circumvent the need for purified protein reagents. At X-Chem, we have developed selection protocols in which library is applied directly to cell lysate. This technique is often the method of choice for projects whose protein is difficult to express, or that require a multi-protein complex to maintain correct fold and function.

FIGURE 1



High-quality protein reagents from Proteros allowed the discovery and characterization of this covalent BTK inhibitor.

ASKING THE RIGHT QUESTIONS IN DEL SELECTIONS

One of the key aspects of DEL-based discovery is its ability to probe specific aspects of selectivity and site-of-action during the screening experiment. Due to its miniaturized format, affinity-mediated selection can be conveniently conducted under a variety of conditions in parallel. These multiplexed selections can provide rich data sets that assess the output compounds across a large number of useful parameters.

The most common and useful parameter examined during DEL selection is selectivity. Tuning out activity against

undesirable but closely related targets is a frequent challenge in target-based drug discovery. Conversely, pan-activity across a number of targets can be therapeutically advantageous, particularly when the related targets are mutants that confer resistance to an established treatment. Both these situations can be effectively addressed by multiplexed DEL selection. One need only conduct selections against the various targets in parallel, and examine the output for overlap or uniqueness across the various selections. At X-Chem, we commonly visualize such an analysis using a bar chart, referred to as a "profile." For a particular chemical series, its enrichment in each selection is represented by the bar height. Selective compounds should only exhibit enrichment at a single target. Poly-selective compounds will show enrichments against a number of targets. Compounds that exhibit a profile consistent with the pharmacological rationale of the project are prioritized for follow-up.

While selection multiplexing of this sort is a powerful tool for discovery of useful ligands, it does come with an important caveat. As discussed in the aforementioned section, in order for the data to be useful, the targets must be of similarly high quality, available at similar concentrations and ideally appended with the same affinity tag. A selection campaign in which the primary target is of high quality, but the various additional targets are not, will have only limited utility in probing questions of selectivity. Therefore, the decision to conduct a multiplexed selection experiment must take into account the additional expense of reagent (or cell lysate) generation. We have found that protein production is a key factor governing the scope of a selection campaign. At X-Chem, we routinely conduct campaigns that contain multiple individual selection conditions.

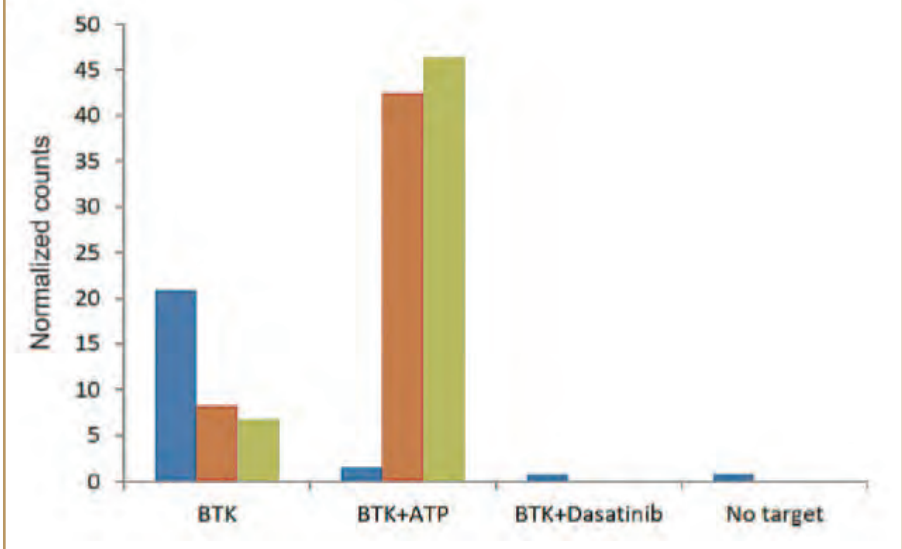
Another parameter that can be conveniently addressed in selection is competitive behavior. By adding a high concentration of a known ligand to a selection, we can saturate a protein's binding site and render it unavailable to library members. Library compounds that are enriched in the apo selection, but absent when the ligand is added, are likely to be competitive with the added ligand. This technique is effective at focusing efforts on ligands that have a high likelihood to be functionally active as they compete with a known functional ligand. On the other hand, library members that do not compete with a known ligand could be potentially allosteric binders. While their functional characteristics cannot be predicted prior to follow-up, they could, if active, represent discovery of a new functional binding pocket on the target.

There are a few factors to keep in mind when designing a competition experiment in DEL selection. The first is the potency and solubility of the added ligand. At X-Chem, we aim to saturate the binding site with a stoichiometric excess of ligand over protein. Because DEL selections are typically run with high protein concentrations (ie, ca. 1 μM), the solubility of the tool compound must usually therefore be greater than 10 μM. For lower affinity ligands, even higher concentrations may be needed. All these factors must be assessed prior to designing the selection experiment.

Interpretation of competitive selection results requires a thoughtful approach. It is commonly assumed that reduced enrichment of library members by added ligands is an indicator of orthosteric competition. It is possible, however, that such behavior can be caused by allosteric communication between the library member binding site and that of the added ligand. This situation is especially likely in proteins, such as GPCRs, in which long-range conformational changes have functional consequences.

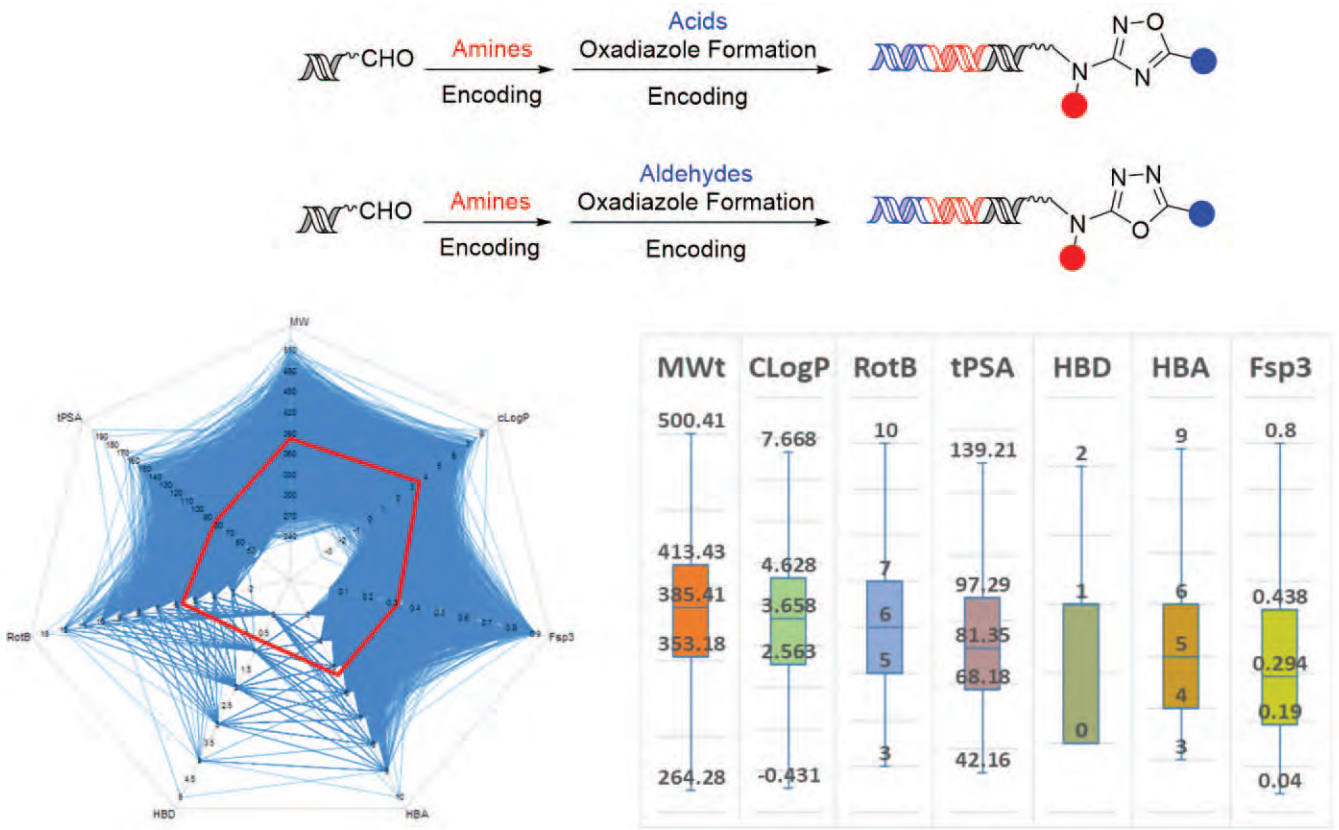
In addition to known inhibitors, competition selection experiments can be conducted using protein binding partners, cofactors, peptides, antibodies, nucleic

FIGURE 2



Example of a profile plot of three separate chemical series across four selection conditions.[5]

FIGURE 3



Structure of two atom-efficient X-Chem libraries and their resulting physicochemical properties.

acids, or any other entities known to bind or otherwise influence the target protein. In some cases, binding to a cofactor or other binding partner is required to organize the target protein into its active conformation. In these cases, one may often observe ligand-dependent enrichment of library members. When the ligand is a substrate or cofactor, then the resulting complex may represent a biologically relevant form of the target.

ENCODED CHEMICAL LIBRARIES & PROPERTIES OF HITS

One of the appealing aspects of DEL screening is that it does not require choosing which chemical matter to search in the selection experiment. The depth of modern sequencing techniques allows the inclusion of all the DELs available to the practitioner. At X-Chem, we include all of our libraries into every selection we conduct. At the analysis stage, however, we do find it useful to prioritize certain classes of chemistry, depending on the needs of the project and the productivity of the selection.

DELs in the past have often suffered from poor physicochemical properties, in particular high molecular weights and calculated lipophilicities. This property inflation was a result of the enthusiasm for DELs with ever-larger numerical size. To obtain libraries with billions of compounds, or more, four-cycle libraries were constructed. Because a typical synthetic cycle will add at least 150 Da of molecular weight, four-cycle libraries have average molecular weights of at least 600 Da, without taking into account cores or other constant moieties in the library. In the early days of DEL, the technology was aimed at intractable targets that had failed in other hit generation approaches. In that context, inflated properties were forgivable being no other platform could provide actionable ligands. As DEL has matured however, it has been increasingly applied to broad portfolios of projects across therapy areas and target classes. In response, DELs need to be designed with a greater focus on physical properties and developability. At X-Chem, our library strategy is focused on atom economy, so that we can deliver lead-like or drug-like matter for most targets. Still, we often observe that many high-value targets only yield to compounds with high molecular weight, lipophilicity and/or peptidic character. Therefore, we also maintain a rich set of peptidic, macrocyclic, and covalent libraries, so that we can be confident that

we will find hits for even the most difficult and previously intractable targets.

X-Chem libraries therefore span a number of chemical classes and property profiles: small and lead-like, drug-like and "beyond rule-of-5." While all libraries are put into a given selection experiment, not all libraries receive equal attention during analysis. Macrocyclic libraries, for instance, would not be prioritized for a typical kinase inhibitor project, unless the project demanded an allosteric inhibitor or some other nonstandard modality. Likewise, it may be not fruitful to focus on lead-like matter for a challenging target like a shallow pocket protein-protein interaction or a highly disordered protein.

ANALYZING THE OUTPUT

DEL technology produces copious quantities of data. A typical selection experiment at X-Chem can easily generate over one billion reads of encoding DNA. These sequences must be translated into the corresponding chemical structural information, clustered on chemical similarity, and profiled across the various selection conditions. While this process provides great depth of understanding of the chemical space selected by the target, it also places great demand on informatics systems. Researchers interested in fully exploiting the power of DEL data need access to a robust and scalable suite of informatics tools.

There are currently no commercial solutions for the analysis of DEL selection data. Various DEL practitioners have implemented bespoke informatic platforms with varying degrees of scalability. At X-Chem, we have created tools that can efficiently mine the 40+ terabytes of data generated by our platform to date. Our tools allow rapid assessment of selectivity and promiscuity, convenient profiling across selection conditions, clustering on chemical similarity and formatting for input into predictive model-building.

SUMMARY

While DEL technology is conceptually straightforward, the successful implementation of this platform requires innovations at all stages. Numerous pitfalls exist that can confound DEL-based lead generation, including suboptimal protein reagents, uninformative selection campaigns, libraries with poor physical properties, and time-consuming analysis. We recommend that researchers looking to exploit this powerful technology partner with an experienced and innovative service provider with a large library of attractive compounds, a fully dedicated suite of informatics tools and, most importantly, a proven track record of success. Even organizations that have an existing DEL platform can benefit from a partner who is driving new innovations in library design, selection science, and informatics. ◆

REFERENCES

1. Goodnow, R. A. Jr.;,Dumelin, C. E.;,Keefe, A. D. Nat. Rev.Drug Discovery (2016); DOI: 10.1038/nrd.2016.213.
2. Ohlmeyer, Michael H. J.; Swanson, Robert N.; Dillard, Lawrence; Reader, John C.; Asouline, Gigi; Kobayashi, Ryuji; Wigler, Michael; Still, W. Clark Proc. Nat. Acad. Sci. U.S.A. 90, 10922-6 (1993).
3. Brenner, Syndey; Lerner, Richard A. Proc. Nat. Acad. Sci. U.S.A. 89, 5381-3 (1992).
4. Zhang, J.-H.; Chung, T. D. Y.; Oldenburg, K. R. J. Biomolec. Screening 4, 67-73 (1999).
5. Cuozzo, John W.; Centrella, Paolo A.; Gikunju, Diana; Habeshian, Sevan; Hupp, Christopher D.; Keefe, Anthony D.; Sigel, Eric A.; Soutter, Holly H.; Thomson, Heather A.; Zhang, Ying; Clark, Matthew A. ChemBioChem 18, 826-33 (2017).

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BIOGRAPHY

Dr. Matthew A. Clark is a world-recognized innovator and leader in the DNA-encoded library (DEL) field. He was part of X-Chem's founding team and served as VP of Chemistry and SVP of research prior to his appointment to the CEO position. Under his scientific leadership, the company developed from a niche chemical discovery platform to a world-leading drug discovery engine serving the biopharma industry. Before joining X-Chem, he was Director of Chemistry at GlaxoSmithKline, where he led the group responsible for design and synthesis of early iteration DELs. He began his professional career at Praecis Pharmaceuticals, where he played a key role in the early development and implementation of technologies that would become the basis for DEL. Dr. Clark is a thought leader in the DEL space, with numerous patents and key DEL publications to his name. He earned his BS in Biochemistry from the University of California, San Diego, his PhD in Chemistry from Cornell University, and conducted post-doctoral studies at the Massachusetts Institute of Technology.

PLATFORM TECHNOLOGY

The Evolution of Cancer Vaccines: Moving Beyond Failure & a New Era for Cancer Treatment

By: Jeremy R. Graff, PhD

INTRODUCTION

Historically, therapeutic vaccines as a viable cancer treatment have had mixed levels of success. Despite strong beginnings with the work of Thiery Boon and his colleagues, who discovered that T cells could recognize proteins from cancerous cells, progress of cancer vaccines diminished after multiple failures using dozens of combinations of antigens, adjuvants, and delivery technologies.[1-3]

Following Boon's research, data from clinical trials evaluating therapies targeting long peptides, minimal epitope peptides and proteins have shown mixed results. With limited understanding of the physiological response that the body naturally produces, treatment has been widely systemic and not targeted, resulting in adverse effects and minimal success in outcomes. Immune cells in the lymph nodes have not been activated specifically to mimic the natural immune response. Also, conventional and chemical adjuvants overwhelmed the system, and targeting heterogeneously expressed antigens had limited success, eventually leading to a pause in cancer vaccine development.[4,5]

Recently, the immuno-oncology landscape has seen a resurgence of vaccines using new methods leveraging the body's natural immune system. New studies show promising data with the use of mRNA-based vaccines and the injection of nanoparticles into regional lymph nodes to achieve disease stabilization.[6] This has led to a potentially groundbreaking era of therapeutic cancer vaccines thanks to discoveries in identifying truncal targets, targeting tumor neoantigens and, notably, developing improved delivery technologies that stimulate a robust, targeted and persistent immune response.

DISCOVERY & CHALLENGE IN DEVELOPING TARGETED CANCER VACCINES

Increased understanding of the immune system and cancer biology has allowed for improved cancer vaccine design. Cancers develop primarily by genetic mutations that result in abnormal and uncontrolled cell growth, driving tumor progression and promoting tumor survival, proliferation, and immune evasion. The successful identification of these "driver mutations" and better understanding of the underlying biological mechanisms enabled the development of more targeted therapies.

Historically, cancer vaccines were developed using peptides derived from tumor-associated antigens (TAAs). TAAs are proteins highly expressed in cancer cells and present on their surface, which allows them to be recognized by T cells during the anti-tumor response.[7] However, this approach can be limited in inducing an effective response and can lead to toxicity issues as some of these antigens are also found on healthy cells, presenting a discrimination challenge to the immune system.

Further research to understand the immunosuppressive and resistant nature of tumors and how they can evade immune surveillance led to the emergence of checkpoint inhibitors (CPIs), which have been successfully implemented in combination with targeted therapies. Unfortunately, some tumors have no or limited response to these treatments even in combination, as cancers can evolve to evade immune recognition. These resistance mechanisms are a challenge in immunotherapies today and partly why many treatments have been unsuccessful in clinical trials. Additionally, the tumor microenvironment (TME) itself can further promote cancer survival.[8] Chronic inflammation can result from an

immunosuppressive TME, further enabling evasion from immune surveillance and promoting cancer progression. A tumor's inflammatory status can also be a predictor of treatment efficiency. CPI treatments may reverse immune suppression of immune inflamed tumors but do not always work. Non-inflamed tumors or "immune-desert" tumors rarely respond to CPIs.

Another limitation with cancer immunotherapy is that patients often have weakened immune systems from prior treatments such as chemotherapy, which means treatments need to be highly effective at stimulating a sustained and potent anti-tumor immune response. This is especially challenging given that cancer is usually diagnosed in older people, where the immune system is slowly declining via a process known as "immunosenescence." This process is caused by changes in the lymph nodes impacting the adaptive and innate immune system functions.[9]

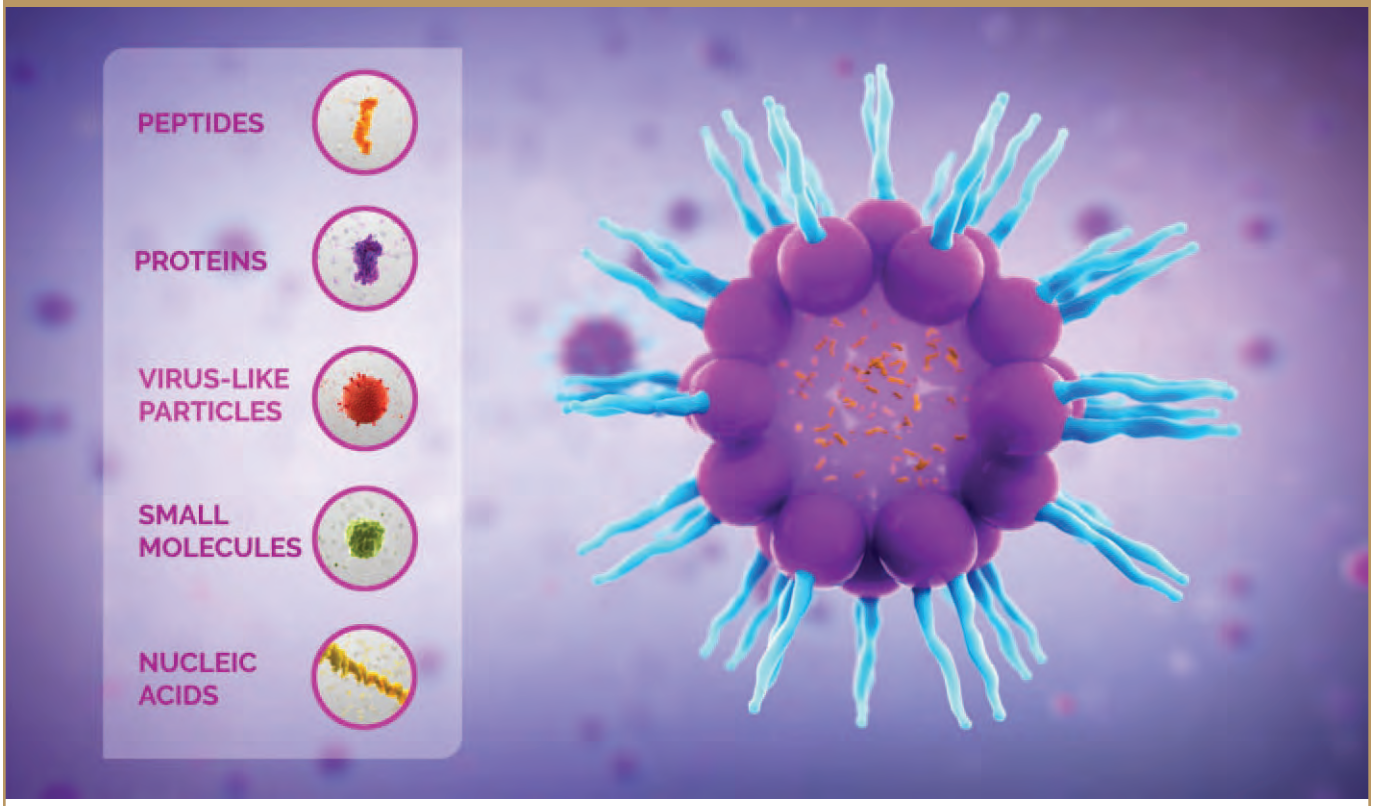
CONSIDERATIONS IN DELIVERY & FORMULATION OF CANCER VACCINES

The addition of immunomodulatory agents such as adjuvants could improve clinical efficacy, especially for antigen targets that are poorly immunogenic. Adjuvants can aid in optimizing immune responses, which can address immunosenescence in elderly patients and cancer patients. In a compromised immune system, with the suppressive TME, adjuvants elicit limited tumor-specific T cell response. Choice of adjuvant must be carefully considered to ensure proper stimulation, potency, and durability of a tumor-specific immune response.

The mechanism of how cancer vaccines are delivered is equally important. Technologies such as viral vectors, oncolytic viruses, and mRNA-based vaccines have all emerged as viable options to facilitate antigen delivery and improve the immune response of vaccine therapies.[10] Other aspects to consider are formulations to facilitate improved delivery of antigens, such as water in oil or oil in water. Each of these treatment options has benefits and drawbacks.

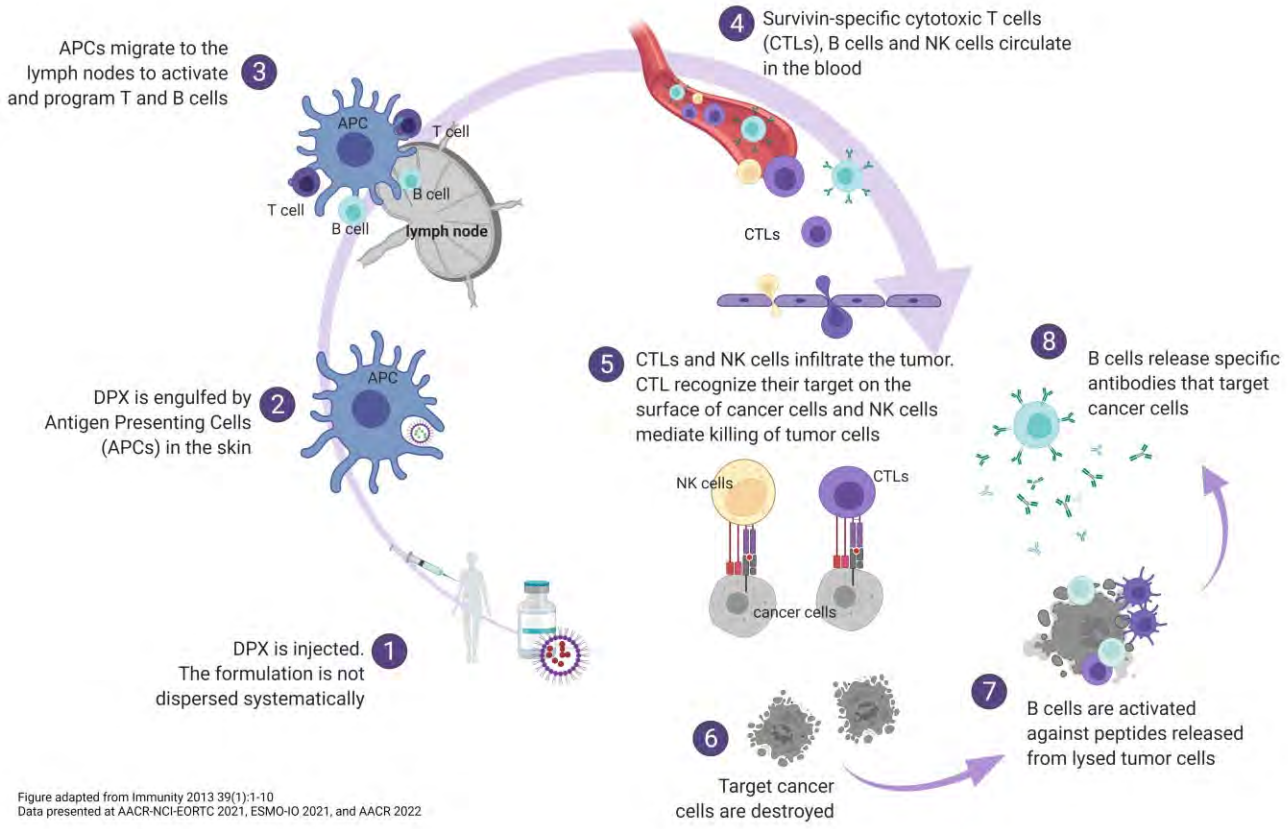
Delivering target antigens to the appropriate innate immune cells must also have the right cues for maturation in order to activate specific T cells. Target antigens should be delivered to antigen presenting

FIGURE 1



The DPX platform is a unique lipid-in-oil, non-emulsion formulation for directed immune response. It is also a versatile delivery technology that can be packed with bioactive molecules, including peptides, proteins, virus-like-particles, small molecules, or nucleic acids. The platform has multiple benefits including controlled release, physiologic immune activation, innate immune stimulation, effective antigen presentation and broad therapeutic application.

FIGURE 2



The DPX therapy can be delivered by simple subcutaneous injection, maintaining the bioactive molecules at the injection site where they interact with antigen-presenting cells, or APCs. APCs take up the DPX vesicles and its cargo and transport them to the lymph nodes to activate T and B cells. These cells can then circulate into the blood, targeting and destroying cancer cells through a specific immune response. This controlled release prevents systemic distribution or leaching of cargo, which can reduce side effects and produce a robust and long-lasting immune response.

cells (APCs) which in turn activate specific T cells and other cells of the innate and adaptive immune system, engaging both T and B cells. To better evoke an effective immune response, cancer vaccines must mimic natural biology and train the immune system to fight off the cancer, which is continuously evolving to evade the immune system.[11]

In cancer vaccine development, researchers need to consider all relevant components for optimal therapeutic efficacy. A vaccine not only needs a precise target to destroy cancer cells and minimize residual disease, but the proper delivery vehicle and adjuvants to induce a long-lasting response in addition to limiting toxicity and adverse events.[12-14] New treatments have emerged, leveraging lessons learned and offering a well-rounded approach by combining target antigens with an optimized delivery technology to induce an appropriate and effective immune response.

A DIFFERENTIATED APPROACH THAT COULD USHER IN A NEW ERA OF CANCER TREATMENT

Today, multiple novel cancer treatment approaches are arising, including the DPX® platform developed by IMV Inc. This delivery technology educates a targeted, robust, persistent immune response in patients by mimicking the physiologic condition of exposing the immune system to a target antigen. The DPX platform is a lipid-in-oil technology that has practical advantages compared to standard emulsions or traditional peptide delivery methods (Figure 1).

Compared to standard emulsions that diffuse payload into surrounding tissues over time, the DPX formulation maintains its cargo in a concentrated volume at the site of injection, where it interacts with immune cells for a prolonged time (Figure 2). This prevents diffusion into tissues and bloodstream while reducing side effects. APCs are recruited and actively uptake the bioactive molecules packaged in DPX. APCs then travel to the lymph node where they activate lymphocytes in a targeted fashion. A robust antigen-specific immune response is elicited, involving T cells, B cells, and natural killer (NK) cells. These

cells then circulate in the blood, infiltrating tumors, destroying only the cancerous cells. Studies have shown that peptides formulated in DPX consistently generate greater T cell responses than in other formulations.[15]

DPX-based therapies stimulate the immune system, leveraging the body's natural mechanisms to fight disease with a comprehensive immune response. These immunotherapies have also shown synergistic effect with checkpoint inhibitors as well as other treatments.

DPX-based therapies can include multiple adjuvants to optimize a prolonged immune response. The DPX platform is versatile and capable of delivering a wide range of bioactive molecules including peptides, proteins, virus-like particles, nucleic acids, mRNA, or other small molecules (Figure 3). One specific drug candidate in development that leverages the DPX platform technology is maveropepimut-S (MVP-S), which incorporates survivin-specific immunogenic peptides to treat cancers. Survivin is a protein commonly expressed in various cancers which promotes aberrant cell growth and contributes to cancer biology. It is a biomarker of poor prognosis and confers resistance to chemotherapy and radiation. Targeting survivin selectively targets only cancer cells and circumvents off-target toxicities, as it is not expressed on normal healthy cells.

Other practical advantages include the delivery path via subcutaneous injection with a simple in-office administration. In addition, DPX-based therapies are fully synthetic and easy to manufacture with long-term stability. Shelf life for DPX-based products can last years compared to aqueous or conventional emulsions, making the supply chain easier to manage.

Given the versatility of the platform, this technology can be applicable in infectious diseases.

CLINICAL TRIALS OF MVP-S VALIDATE THE POTENTIAL OF THE DPX PLATFORM

IMV is evaluating DPX-based assets in several clinical trials in difficult-to-treat cancer indications, including diffuse large B-cell lymphoma (DLBCL), ovarian, breast, and bladder cancer. Previous studies have shown encouraging results, notably in patients who have failed on prior lines of therapy. MVP-S is the clinical validation and proof of concept of the DPX platform's potential in hematologic and solid cancer indications with and without CPIs.

MVP-S has demonstrated a specific anti-tumor immune response along with a favorable safety profile. Recent findings from IMV's Phase 2 clinical trial, DeCidE1, which examined MVP-S with intermittent low dose cyclophosphamide (CPA) in patients with advanced, recurrent ovarian cancer, suggest that immunogenic tumors are more susceptible to MVP-S treatment. Around 70 percent of patients diagnosed with ovarian cancer will have a recurrence.[16] Notably, most patients in the DeCidE1 study had been heavily pretreated and specifically 57.9% were platinum resistant but responded to the MVP-S treatment. The trial has proven the mechanism of action of MVP-S elicits a robust immune response that involves T, B, and NK cells. These results support additional clinical studies of MVP-S in ovarian cancer. The company has recently dosed its first patient in the AVALON trial, an open label, multi-center, Phase 2b study evaluating MVP-S with intermittent, low-dose CPA in patients with platinum-resistant ovarian cancer.

TABLE 1

	DPX™ Delivery	Aqueous Delivery	Conventional Emulsions
Particle Size	Homogeneous 5-10nm	Heterogeneous <50nm	Heterogeneous <100nm
Stability at 5°C	>3 years	Minutes to hours	Days to months
Leakage from SoI*	No	Immediate	Gradual
Immune Uptake	Active via APCs	Active and passive	Active and passive
LN Targeted/ Trafficked	Yes	No	No

The DPX platform has multiple advantages compared to traditional peptide delivery. The formulation retains cargo at the SoI with an extended release, which is distinct from emulsions that leach cargo over time. This drives recruitment of immune cells to the SoI, promoting active uptake of cargo via APCs and flow through LNs. Additionally, the DPX formulation is shelf stable at room temperature for up to 3 years.
***SoI = Site of Injection, LN = Lymph Node, APCs = Antigen Presenting Cells.**

Another Phase 2 trial, SPiReL, evaluating MVP-S/CPA and pembrolizumab in subjects with recurrent/refractory DLBCL (r/r DLBCL), has also shown clinical benefit in patients. DLBCL remains the most common non-Hodgkin's lymphoma with a 5-year survival rate of about 64%. The results of the SPiReL trial specifically showed long duration of clinical benefit in 77.8% of evaluated patients and survivin-specific T cell responses with a favorable safety profile. Building off these promising results, a second open label, multi-center, Phase 2b trial, VITALIZE, is currently being conducted evaluating MVP-S/CPA in combination with pembrolizumab in patients with r/r DLBCL.

Finally, a Phase 2 "basket" trial evaluating MVP-S/CPA in combination with pembrolizumab in multiple cancers showed promising results in tumors positive for the microsatellite instability high biomarker, as well as bladder cancer patients. In metastatic bladder cancer, MVP-S has induced robust survivin-specific T cell responses and was shown to provide clinical benefit in patients who had previously received prior immune checkpoint inhibitor therapy, making MVP-S a potentially promising treatment option.

In conclusion, MVP-S offers many unique and advantageous properties to educate the immune system and promote a robust, targeted, and persistent immune response. DPX-based therapies, such as MVP-S, uniquely mimic the physiologic condition of exposing the immune system to a target antigen. As a novel immune educating platform, DPX offers:

- Targeted and physiologic delivery of payload to lymph nodes
- Effective antigen presentation and uptake
- Robust T cell activation and innate immune stimulation and recruitment
- Potentially unprecedented clinical datasets
- Versatility to deliver a wide range of cargo
- Plug-and–play platform that can be leveraged across oncology, and across therapeutic areas to deliver appropriate cues to the immune system

Despite the many challenges researchers have faced in identifying effective, targeted, non-toxic cancer vaccine treatments, guided by the historical findings and advancements made in the therapeutic cancer vaccine landscape, the DPX platform has shown promising potential for cancer treatment and offers a unique approach in immunotherapy to elicit a targeted immune response and bolster patient quality of life. ◆

REFERENCES

1. van der Bruggen, P., Traversari, C., Chomez, P., Lurquin, C., De Plaen, E., Van den Eynde, B., Knuth, A., & Boon, T. (1991). A gene encoding an antigen recognized by cytolytic T lymphocytes on a human melanoma. Science, 254(5038), 1643–1647. https://doi.org/10.1126/science.1840703.
2. Coulie, P. G., Karanikas, V., Colau, D., Lurquin, C., Landry, C., Marchand, M., Dorval, T., Brichard, V., & Boon, T. (2001). A monoclonal cytolytic T-lymphocyte response observed in a melanoma patient vaccinated with a tumor-specific antigenic peptide encoded by gene MAGE-3. Proceedings of the National Academy of Sciences, 98(18), 10290–10295. https://doi.org/10.1073/pnas.161260098.
3. Rosenberg, S. A., Yang, J. C., Schwartzentruber, D. J., Hwu, P., Marincola, F. M., Topalian, S. L., Restifo, N. P., Dudley, M. E., Schwarz, S. L., Spiess, P. J., Parkhurst, M. R., Kawakami, Y., Seipp, C. A., Einhorn, J. H., & White, D. E. (1998). Immunologic and therapeutic evaluation of a synthetic peptide vaccine for the treatment of patients with metastatic melanoma. Nature Medicine, 4(3), 321–327. https://doi.org/10.1038/nm0398-321.
4. Chow, S., Berek, J. S., & Dorigo, O. (2020). Development of therapeutic vaccines for ovarian cancer. Vaccines, 8(4), 657. https://doi.org/10.3390/vaccines8040657.
5. Rosenberg, S. A., Yang, J. C., & Restifo, N. P. (2004). Cancer immunotherapy: Moving beyond current vaccines. Nature Medicine, 10(9), 909–915. https://doi.org/10.1038/nm1100.
6. Sahin, U., Derhovanessian, E., Miller, M., Kloke, B.-P., Simon, P., Löwer, M., Bukur, V., Tadmor, A. D., Luxemburger, U., Schrörs, B., Omokoko, T., Vormehr, M., Albrecht, C., Paruzynski, A., Kuhn, A. N., Buck, J., Heesch, S., Schreeb, K. H., Müller, F., … Türeci, Ö. (2017). Personalized RNA mutanome vaccines mobilize poly-specific therapeutic immunity against cancer. Nature, 547(7662), 222–226. https://doi.org/10.1038/nature23003.
7. Wagner, S., Mullins, C. S., & Linnebacher, M. (2018). Colorectal cancer vaccines: Tumor-associated antigens vs neoantigens. World journal of gastroenterology, 24(48), 5418–5432. https://doi.org/10.3748/wjg.v24.i48.5418.
8. Sacdalan, D. B., & Lucero, J. A. (2021). The Association Between Inflammation and Immunosuppression: Implications for ICI Biomarker Development. OncoTargets and therapy, 14, 2053–2064. https://doi.org/10.2147/OTT.S278089.

9. Cuzzubbo, S., Mangsbo, S., Nagarajan, D., Habra, K., Pockley, A. G., & McArdle, S. (2021). Cancer Vaccines: Adjuvant Potency, Importance of Age, Lifestyle, and Treatments. Frontiers in immunology, 11, 615240. https://doi.org/10.3389/fimmu.2020.615240.
10. Miao, L., Zhang, Y., & Huang, L. (2021). mRNA vaccine for cancer immunotherapy. Molecular cancer, 20(1), 41. https://doi.org/10.1186/s12943-021-01335-5.
11. Sellars, M. C., Wu, C. J., & Fritsch, E. F. (2022). Cancer vaccines: Building a bridge over troubled waters. Cell, 185(15), 2770–2788. https://doi.org/10.1016/j.cell.2022.06.035.
12. Cuzzubbo, S., Mangsbo, S., Nagarajan, D., Habra, K., Pockley, A. G., & McArdle, S. (2021). Cancer Vaccines: Adjuvant Potency, Importance of Age, Lifestyle, and Treatments. Frontiers in immunology, 11, 615240. https://doi.org/10.3389/fimmu.2020.615240.
13. Hailemichael, Y., Dai, Z., Jaffarzad, N., Ye, Y., Medina, M. A., Huang, X. F., Dorta-Estremera, S. M., Greeley, N. R., Nitti, G., Peng, W., Liu, C., Lou, Y., Wang, Z., Ma, W., Rabinovich, B., Sowell, R. T., Schluns, K. S., Davis, R. E., Hwu, P., & Overwijk, W. W. (2013). Persistent antigen at vaccination sites induces tumor-specific $CD8^+$ T cell sequestration, dysfunction and deletion. Nature medicine, 19(4), 465–472. https://doi.org/10.1038/nm.3105.
14. Saxena, M., van der Burg, S. H., Melief, C., & Bhardwaj, N. (2021). Therapeutic cancer vaccines. Nature reviews. Cancer, 21(6), 360–378. https://doi.org/10.1038/s41568-021-00346-0.
15. Bramhecha, Y., Dorigo, O., Kaliaperumal, V., Torrey, H., Ebrahimizadeh, W., Patterson, K., Dirk, B., Bydoun, M., Kennedy, B., Lobo, A., Weir, G., Graff, J., Fiset, S., & Hrytsenko, O. (2021). Abstract LBA026: Survivin peptides formulated in the DPX delivery platform rather than standard emulsions, elicit a robust, sustained T cell response to survivin in advanced and recurrent ovarian cancer patients. Poster Presentations - Late-Breaking Proffered Abstracts. https://doi.org/10.1158/1535-7163.targ-21-lba026.
16. Ovarian cancer recurrence and treatment. OCRA. (n.d.). Retrieved May 19, 2022, from https://ocrahope.org/patients/about-ovarian-cancer/recurrence/.

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BIOGRAPHY

Dr. Jeremy Graff is the Chief Scientific Officer of IMV Inc. and brings more than 20 years of experience in preclinical and clinical research and translational analysis for novel immune-activating therapeutics in oncology. Most recently, Dr. Graff served as Chief Development Officer and Senior Vice President, Research at HiberCell, a biotechnology company developing novel therapeutics for cancer relapse and metastasis. He led the scientific and clinical development teams for HiberCell. Prior to that he was employed at Biothera Pharmaceuticals serving as President since 2018 and Chief Scientific Officer since 2014. In these executive roles, he implemented strategic translational studies along with clinical programs in immuno-oncology. He also managed corporate strategy for investor engagement and oversaw the acquisition of Biothera's lead asset Imprime PGG by HiberCell, Inc in 2020. Dr. Graff spent 16 years at Eli Lilly and Lilly Research Labs, where he developed extensive experience in cancer drug discovery and development, immuno-oncology, biomarker discovery, and patient stratification. During his last position at Eli Lilly as Group Leader, Cancer Biology and Patient Tailoring, he established a Translational Oncology Unit to improve the technical success of clinical trials. At Lilly Research Labs, he was the recipient of President's Recognition Award, the company's highest annual award. Dr. Graff earned his PhD from the University of Kentucky's Markey Cancer Center and completed a post-doctoral fellowship at the John Hopkins University Oncology Center. He has authored 60 peer-reviewed publications and holds a number of patents for novel cancer therapies.

NANOPARTICLE ENGINEERING

Lighting the Way to a Patient-Centric Future

By: Christopher Worrall, PhD

INTRODUCTION

When developing a new drug, a strong focus is placed on ensuring the compound is effective, safe, and feasible to manufacture at scale. These are all important concerns. However, it is crucial to bear in mind that a drug's impact goes far beyond its chemistry. While a drug may be able to achieve its objective perfectly, if it is unpalatable, difficult to swallow, or results in a multitude of side effects, patient compliance will suffer. Put simply, if an efficacious drug is not taken, it will not be effective.

As a result, medication adherence is widely recognized as an increasingly relevant issue in healthcare. Poor adherence to therapy naturally results in worse patient outcomes and can also place an economic strain on the healthcare system. This issue is especially notable for geriatric and pediatric patients.

Enhancing the properties of drugs to make them more convenient for patients, with potentially fewer side effects or a smaller pill size, could significantly impact a patient's quality of life. One way to accomplish this is by utilizing the latest technologies to enhance the properties of both new and existing drugs. In particular, nanoparticle engineering technologies could help improve compliance and patient outcomes, for both small-molecule and biological drugs. The following will discuss how nanotechnology can help facilitate a shift toward more patient-centric medicine.

CHALLENGES FACED BY PATIENTS

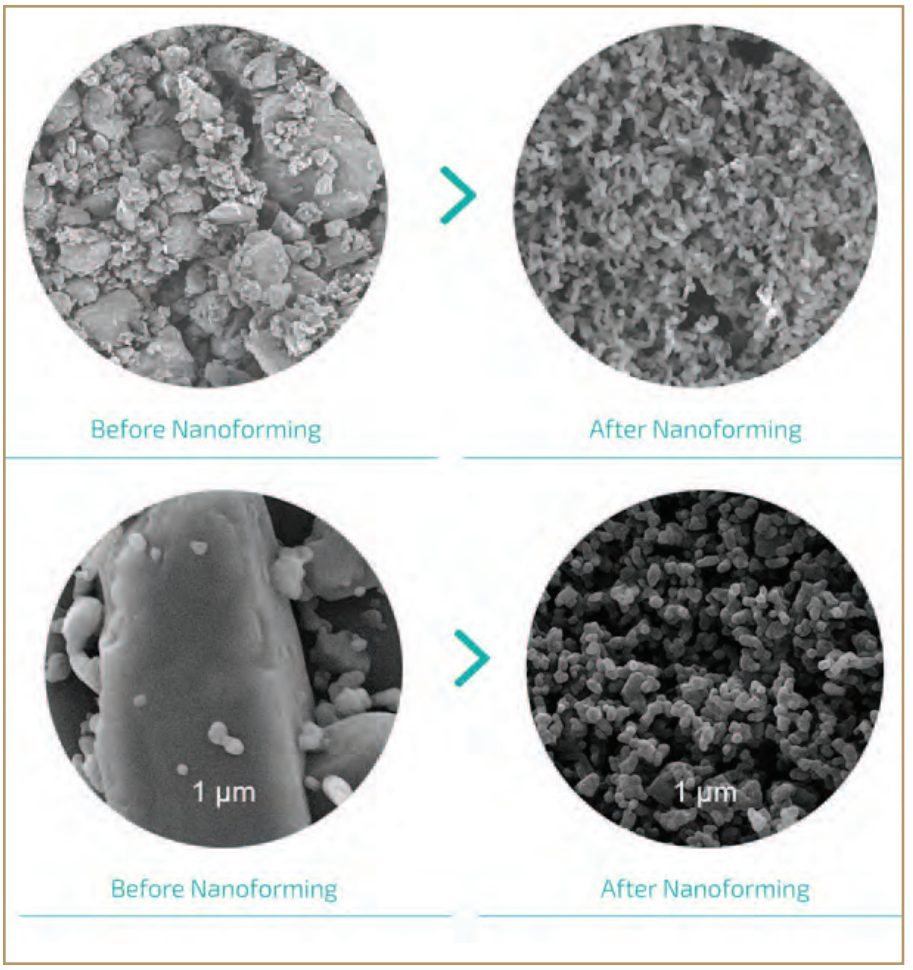
Elderly patients often have complex drug regimens, with a variety of side effects that must be managed. Mobility is also a significant challenge amongst the geriatric community. Medicines that cannot be self-administered and require hospital visits cause great inconvenience and reluctance among patients.

With the number of older persons aged 60 or over is expected to double by 2050, the impact of non-compliance among the elderly is only expected to grow.[1] Advances in biological delivery devices and biological nanoparticles that allow a higher drug concentration could be of use here. Meanwhile, children may not understand the need to take an unpleasant-tasting medicine, and their reluctance can result in non-compliance. It has been estimated that a third of pediatric patients fail to complete even relatively short-term drug regimens.[2] Treatment sessions for chronic conditions that require children to frequently visit a hospital can also result in significant disruptions to everyday life and absences from school. As a result, there are very clear quality-of-life benefits to be gained when the pharmaceutical community places the patient first and foremost during drug development.

OBSTACLES IN THE WAY OF PATIENT-CENTRIC MEDICINES

In order for more patient-centric drugs to reach the market, a number of challenges must be overcome during development. For instance, systemic circulation of drugs can result in more side effects compared to a product delivered locally to the therapeutic target, for example, treating an ophthalmic disorder through topical eye drops. However, biological membranes in the eye can prevent local delivery of drugs. Equally, treating a lung disorder through an inhaled therapy would in some cases be ideal. However, for drugs to penetrate the lung, they must possess the correct aerodynamic parameters, which requires them to be 1 to 5 microns in size, ideally. Technologies that can facilitate this and other local drug delivery could allow more patient-centric, localized therapies to reach the market.

Additionally, a trend toward more complex and, conse-



quently, poorly soluble new drug candidates means many life-changing drugs never reach the patients who need them. Low aqueous solubility leads to poor absorption in the body and subsequently poor bioavailability, defined as the extent and rate of drug entering systemic circulation.[3] This can mean a drug will not reach its target area in sufficient quantities to achieve a therapeutic effect. Poor solubility is a leading cause of failure in drug development, with up to 90% of new drug candidates falling within the Biopharmaceutical Classification System (BCS) low solubility categories.[4]

The latest nanoparticle engineering technologies promise to address these challenges and more, improving care for patients around the world.

NANOPARTICLE-BASED APPROACHES FOR PHARMACEUTICAL DEVELOPMENT

Nanoparticle engineering approaches work by shrinking down the size of drug particles to improve their pharmacokinetic properties or to help them access challenging drug delivery routes.

In principle, the smaller the particles, the greater the surface-area-to-volume ratio of the active pharmaceutical ingredient (API). Put simply, as the API particles reduce in size, their surface area increases, leading to greater interaction with the solvent and improved solubility. For example, crystals of aprepitant (an NK-1 tachykinin receptor antagonist used to treat chemotherapy-induced nausea) exhibit a 41.5-fold increase in surface area, when particle size changes from 5 µm to 120 nm.[5]

There are a number of nanoparticle engineering approaches that capitalize on this effect and can be used to create small molecule nanoparticles, including the following:

- Nanomilling is a technique that works by milling in a liquid medium. It can successfully reduce drug particles to the range of 100s of nm in some cases. However, mechanical energy is used to break up the crystals into smaller sizes, which raises surface free energy. And may cause defects in the crystal lattice and amorphous regions. Such domains could also lead to differences in dissolution and, therefore, potential variability in therapeutic response for patients.

- Spray drying is another popular method for particle size reduction, typically micron-sized. This approach transforms a fluid material into a dried powder by spray-drying APIs with a polymer, which prevents the API particles from interacting with each other, to create an amorphous solid. While effective for certain applications, the polymer can add significant weight to the preformulated material, making it more challenging to form products at the intended dose and in the desired format.

- Controlled Expansion of Supercritical Solutions (CESS) technology has emerged as an alternative, game-changing solution to the challenge of poor solubility and patient-centricity in BSC Class II and IV molecules. Particles are dissolved in supercritical carbon dioxide ($scCO_2$) and crystallized under controlled temperature and pressure,

without excipients. The process is scalable, and allows uniform particles of tunable size, shape, and polymorphic form to be produced in the low nanoscale range. In addition, as this approach makes use of green $scCO_2$ as its solvent, it is environmentally friendly and can help to reduce the manufacturing footprint.

CREATING NEW AVENUES FOR PATIENT-CENTRIC DRUG DELIVERY

Using the CESS® process, it is possible to create small-molecule nanoparticles as small as 10 nm in some cases – potentially small enough to cross the blood-brain barrier, which is ordinarily impassable. Designed to shield the brain from toxic substances in the blood, epithelial-like tight junctions within the brain capillary endothelium block the passage of approximately 98% of small molecule drugs, and most biologics.[6] As a result, nanoparticle engineering could open up new drug targets, creating exciting possibilities for treating debilitating central nervous system (CNS) disorders such as Alzheimer's and Parkinson's.

Meanwhile, many diseases of the lung, such as such as asthma, emphysema, chronic obstructive pulmonary disease (COPD), cystic fibrosis, primary pulmonary hypertension, and cancer, are prime candidates for local delivery. This can help avoid first-pass metabolism in addition to avoiding systemic side effects by depositing directly at the site. In the case of the lung, particles smaller than 1 μm tend to be exhaled due to their low inertia, while particles larger than 5 μm can struggle to reach the deep lung. Nanoparticles can be clustered to create larger particles in the ideal 1-5-μm aerodynamic range, allowing them to penetrate the periphery of the lung and create new possibilities for improved inhaled therapies to treat respiratory disorders.[7]

The eye presents another challenge. Topical administration is an ideal route for ophthalmic delivery. In this case, systemic delivery would require a relatively high circulating drug concentration for a therapeutically effective dose to reach the eye, so topical medicines can have significantly reduced side effects by comparison.[8] However, high tear-fluid turnover rate and nasolacrimal drainage rapidly remove fluid from the eye, meaning a drug's bioavailability must be high for it to be effective.

Physiological barriers designed to prevent entry of toxic chemicals, such as the corneal epithelia, present another complication in the way of ophthalmic delivery. By reducing the size of drug particles to increase their permeability across these barriers, as well as improving their bioavailability, nanoparticle engineering can potentially provide an ideal way forward for topical ophthalmic therapies struggling under the weight of these obstacles.

LOWER DOSE; HAPPIER PATIENTS

In addition to creating new avenues for drug delivery, reducing drug particle size to the extent that the CESS® process can opens up a variety of opportunities to transform the patient experience. By reducing particle size to the nanoscale, and eliminating the need for bulky excipients to stabilize nanoparticles, the consequent upsurge in dissolution rate and bioavailability could mean that a lower dosage and regimen can achieve the same therapeutic effect. This would mean the number of pills a patient has to take in a day, referred to as pill burden, could be reduced – a significant patient benefit.

In addition to addressing pill burden, lowering the dose of API needed could also help to reduce the size of the pill. With difficulty swallowing, known as dysphagia, affecting an estimated 9 million people in the US alone and disproportionately affecting the elderly, children, and those with certain medical conditions that make swallowing more challenging, this benefit has the potential to positively impact many lives.[9] Lowering the dose can also help reduce adverse side effects, enhancing quality of life – especially for patients taking multiple medications. Taken together, the impact of lowering the dose has the potential to increase medical compliance across the board.

BROADENING THE BIOLOGICS FIELD

The biologics market is growing rapidly. Valued at approximately $302.63 billion in 2020, it is expected to reach $509.23 billion by 2026.[10] Derived from natural sources and encompassing therapeutic proteins and other large biomolecules, as well as nucleic acid (DNA and RNA)-based therapies, the growth in the biologics field can be partially attributed to their potency, high specificity and safety profiles. This makes them excellent candidates for patient-centric therapeutics.

However, developing biological drugs presents its own unique challenges. While many biological drugs are water soluble, their large size can make accessing a drug

delivery route challenging due to their inability to cross barriers in the body. In addition, biologics often struggle with stability due to a tendency for particles to aggregate. Any process applied to them must also avoid negatively impacting biological activity – for example, enzymes cannot be exposed to high temperatures or they could lose their activity.

The latest nanoparticle engineering technology could offer a means to help biological drugs reach their full potential. By reducing the size of biological particles to as low as 50 nm without necessitating high temperatures, shear stresses, or damaging biological activity, it may be possible for them to access new drug delivery routes that were previously barred. For instance, a collaboration between Nanoform and Herantis is currently investigating whether a therapeutic compound for Parkinson's disease, HER-096 (a synthetic chemical peptidomimetic version of the active parent CDNF protein), can be delivered to the brain through the oral route. If successful, this could be game-changing in the search for a cure to this debilitating disease.

LOOKING TO THE FUTURE

In light of the latest technologies, the future of patient-centric medicines looks bright. Patient-centricity is an increasing focus in the pharma industry, and this is only expected to continue moving forward. This is reflected by the updated ICH Q8, Q9, and Q10 guidelines, which focus in part on the needs of the patient and for quality by design (QbD) to ensure the quality of therapeutics. The shift toward patient-centricity is driven not only by an aging population, but also by advances in digital health technology that provide key insights into patients' comfort. This makes it easier than ever to incorporate feedback that can improve treatment. Collaboration within the industry to bring together data, enabling technology, and pharmaceutical problem solvers are keys to enabling more patient-centric care. By partnering to leverage advanced technologies such as nanoparticle engineering during drug development, patient compliance and comfort can be dramatically increased.

From young to old, patients around the world stand to benefit from more patient-friendly medicines with fewer side effects, higher drug loads, and patient-friendly administration routes. Ultimately, this can both ease the burden of poor medication adherence on the healthcare system and improve quality of life. ◆

REFERENCES

1. https://www.who.int/news-room/fact-sheets/detail/ageing-and-health
2. https://publications.aap.org/pediatrics/article-abstract/115/6/e718/67454/How-Do-You-Improve-Compliance?redirectedFrom=fulltext.
3. https://www.ncbi.nlm.nih.gov/books/NBK557852/.
4. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4629443/.
5. https://pubmed.ncbi.nlm.nih.gov/17601629/.
6. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3494002/.
7. https://onlinelibrary.wiley.com/doi/epdf/10.1002/med.20140.
8. https://jpet.aspetjournals.org/content/370/3/602.
9. https://pubmed.ncbi.nlm.nih.gov/25193514/.
10. https://www.mordorintelligence.com/industry-reports/biologics-market

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BIOGRAPHY

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TOP SPRAY GRANULATION

POLYOX™: Producing Lightweight Metformin Hydrochloride Extended-Release Tablets for Patient Adherence & Cost-Effective Manufacturing

By: Atul Lohade, PhD, Vinay Muley, and Tejas Gunjikar, PhD

INTRODUCTION

In recent years, drug development has been trending toward reducing tablet weight while maintaining similar drug performance to improve patient adherence. Reducing tablet weight is especially prevalent in the formulation of Metformin Hydrochloride extended-release tablets, which are widely used in long-term Type II diabetes treatment. While Metformin Hydrochloride tends to be efficaciously delivered via extended-release tablets, this delivery format usually leads to larger tablets that are difficult to swallow, thereby increasing the risk of reduced patient compliance.[1]

Patient noncompliance contributes to 50% of all treatment failures and adds billions of dollars to healthcare costs worldwide.[2] Smaller, lighter tablets with better drug delivery design have the power to solve this problem and boost patient adherence. However, formulating smaller extended-release tablets can be challenging, expensive, and time-consuming. Often, drug developers struggle with controlling the drug release of a smaller tablet at a definite rate. Understanding the challenges associated with developing smaller extended-release tablets, and the excipient-based solutions to these challenges, will empower formulators to develop robust, stable drug formulations with high patient adherence while cutting manufacturing costs.

THE STUDY

Today, commercially available Metformin Hydrochloride extended-release tablet formulations are generally based on matrix technology or osmotic controlled-release technology. Drug manufacturers can simplify the production of these extended-release tablets by using top-spray granulation processes.

While POLYOX™ — an excipient with a granular or spherical morphology — is generally used during high-shear granulation techniques, this study explores the development of POLYOX-based Metformin Hydrochloride extended-release tablet formulation via top-spray granulation to achieve ease of dosing and cost-effective manufacturing. During the study, IFF Pharma Solutions investigated the development of metformin hydrochloride extended-release tablets (500 mg) by top-spray granulation processes and the compaction properties of the developed granules.

BACKGROUND

Various aspects of granulation — such as optimal addition rate of binder solution, impeller and chopper speed, wet-massing time, and milling of dried granules — impact the manufacturing process and should be studied carefully for successful development.[3] High-shear granulation increases manufacturing steps, time, and cost, while top-spray granulation provides the advantage of simultaneous granulation and drying in the same equipment, making it a great choice for continuous manufacturing.

TABLE 1

Sr. No.	Ingredients	Quantity per tablet (mg)		
		F1	F2	F3
Intra-granular				
1	Metformin Hydrochloride	500.0	500.0	500.0
2	**POLYOX™ WSR Coagulant**	**100.0**	**130.0**	**160.0**
3	METHOCEL™ E5 Premium LV	6.0	6.0	6.0
4	Purified Water	q.s.	q.s.	q.s.
Extra-granular				
5	Magnesium stearate	4.0	4.0	4.0
Dissolution at 3 hours (USP specification- 45 to 65%) {Dissolution Media: Phosphate buffer, pH 6.8, USP apparatus type I (basket) 100rpm}				
% Drug release		90	70	58

Composition Optimization of Metformin Hydrochloride Extended-Release Tablets

Pharmaceutical manufacturers should remain aware of some of the potential challenges of the top spray granulation process. Excessive temperature or moisture could cause agglomeration of POLYOX, leading to particles sticking to the fluid bed processor's (FBP) internal surfaces, including the base plate. Air blockage may cause uneven temperatures and air distribution, which can lead to an agglomeration of particles and an unfeasible batch.

In this investigation, low tablet weight POLYOX-based Metformin Hydrochloride extended-release tablets were developed, and the compaction properties of the granules were evaluated.

MATERIALS

POLYOX water-soluble polymers for pharmaceutical applications possess a unique set of properties that allow for distinctive drug delivery solutions. They exhibit many properties typical of other classes of water-soluble polymers, including lubricity, binding, water retention, thickening, and film formation. Supplied in a wide range of molecular weights to meet specific formulation and processing requirements, the advantages of POLYOX include fast hydration, rapid swelling, thermoplastic properties, superior adherence, and more.

They are free-flowing hydrophilic powders supplied in a variety of viscosity grades corresponding to approximate molecular weight, ranging from 100,000 to 7,000,000 Daltons; this versatility has made POLYOX a popular choice for many pharmaceutical applications, especially when it comes to managing tablet weight. Typically, used as an excipient in controlled-release formulations, POLYOX can also provide a robust matrix-based system when formulating smaller tablet weights and sizes via top-spray granulation.

Materials used in development include Metformin Hydrochloride, and various grades of POLYOX WSR polymers, Hypromellose (METHOCEL™ E5 Premium LV), and Magnesium stearate.

METHODS

Development of Metformin Hydrochloride Extended-Release Tablets (500 mg)

To prepare lightweight Metformin Hydrochloride extended-release tablets for the dissolution study, researchers sifted Metformin Hydrochloride and POLYOX WSR Coagulant through No. 20 mesh and loaded them in GPCG 1.1 top-spray bowl. The blend was granulated using METHOCEL E5 Premium LV dissolved in purified water. The process parameters for FBP

TABLE 2

Sr. No.	Parameters		Observation
1	Bulk Density (g/mL)		0.36
2	Tapped Density (g/ mL)		0.51
3	Compressibility Index (CI)		30.00
4	Hausner's Ratio (HR)		1.41
5	Particle Size Distribution (% retain)	#60 ASTM	16.8
		#100 ASTM	27.2
		Collector	56.2

Micromeritic Properties of Metformin Hydrochloride Extended-Release Granules (F3 composition)

TABLE 3

Time (hours)	USP Specification	Initial	1 M	3M	6M
Drug Release (% dissolved)					
1	20 to 40	37.4	36.9	37.1	37.4
3	45 to 65	62.8	62.3	62.7	62.6
10	NLT 85	89.9	89.5	89.7	89.6

Comparative Dissolution of the Metformin Hydrochloride Extended-Release Tablets (500 mg) (F3 composition)

top-spray granulation monitored include product temperature in the range of 30°C to 40°C, spray rate 3 to 7 g/min, and drive speed in the range of 20 to 40 m^3/h.

The granules were then blended with lubricant magnesium stearate using a double cone blender (Bowman Archer Ltd), and tablets containing 670 mg of granules were compressed using a circular 12-mm punch on a single rotary compression machine (Kambert Engg. Pvt Ltd). Compressed tablets were then evaluated for physical attributes like hardness and thickness.

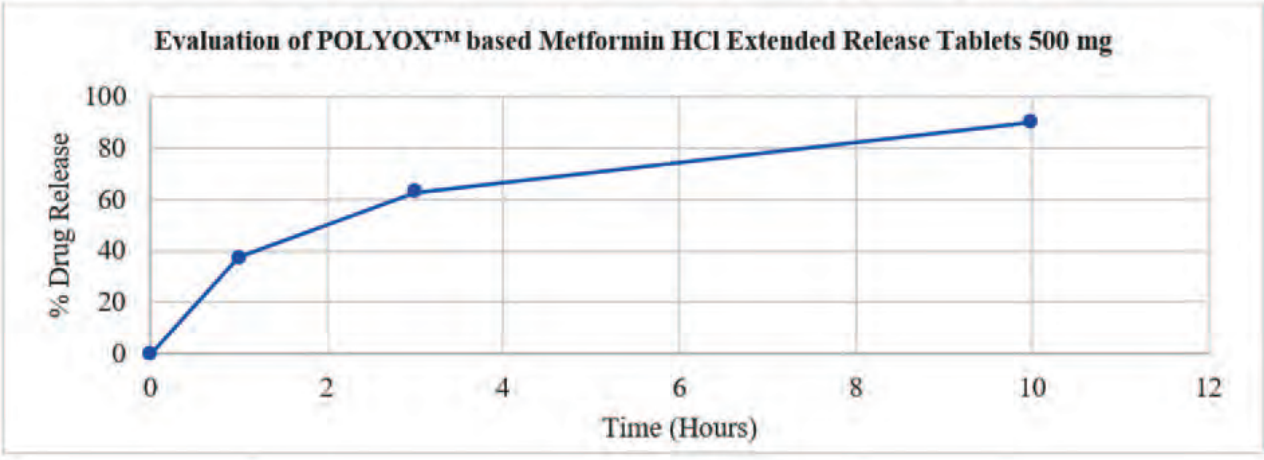
For the dissolution of Metformin Hydrochloride extended-release tablets (500 mg), researchers carried out *in vitro* studies to optimize the formulation and evaluate the performance of the finished product. For dissolution, test, and specification listed in Metformin Hydrochloride extended-release tablets monograph of USP pharmacopeia was followed.[4] The Dissolution condition consists of 900 ml of 6.8 pH phosphate buffer media in USP type I apparatus (basket method) at 100 rpm.

Researchers evaluated the stability performance of the POLYOX-based Metformin Hydrochloride extended-release tablets (500 mg). Tablets were packed in a triple laminated pouch and charged on stability condition at 40°C/75% RH (stability chamber by Neutronics equipment company Ltd.). Dissolution was performed at different time intervals (1, 3, and 6 months) and was compared with the initial release data.

Compaction Study

The compaction properties of different grades of POLYOX and POLYOX-based Metformin Hydrochloride extended-release granules were studied using a compaction simulator (ESH compaction simulator, UK). The tablet compression was carried out with a 13-mm flat, D-type tooling punch, and the physical evaluation of the compressed tablets (viz, hardness, thickness, and diameter) was performed after 24 hours of storage at ambient temperature and controlled humidity. Researchers calculated the tensile strength for each tablet from obtained hardness, thickness, and diameter of the tablet, then plotted it against the compression pressure.

FIGURE 1



Dissolution Study of the Metformin Hydrochloride Extended-Release Tablets (500 mg) (F3 composition)

RESULTS & DISCUSSION

Development of Metformin Hydrochloride Extended-Release Tablets (500 mg)

The composition was optimized and screened for the quantity of controlled release polymer (POLYOX WSR Coagulant) to obtain the desired release profile at 3 hours (Table 1).

The dissolution study showed that, as the concentration of the POLYOX WSR Coagulant increased, the drug release was decreased at 3-hour intervals. F3 formulation showed the desired drug release, therefore the same was used for further studies. The top-spray granulation process was satisfactory and did not show any processing challenges like agglomeration and uneven distribution of the binder. Physical properties observed for the granules (F3) are shown in Table 2.

Flow property data showed the poor flow of the granules. Particle size distribution of the granules (Table 2) suggested increased fine proportion as compared to the granular portion. This can be attributed to a higher proportion of the API (Metformin Hydrochloride) present in the composition (~75% w/w).

Lubricated granules were subjected to compression using round shape punches. The compression process was found satisfactory, and the finished product did not show any tablet defects – physical parameters were observed for the compression process.

The results reflected white to off-white round tablets with an average weight of 670 mg. The diameter of the tablet was 12 mm, and the thickness was reported to be 6.10 to 6.20 mm. Researchers found the hardness to be about 5 to 6 kP.

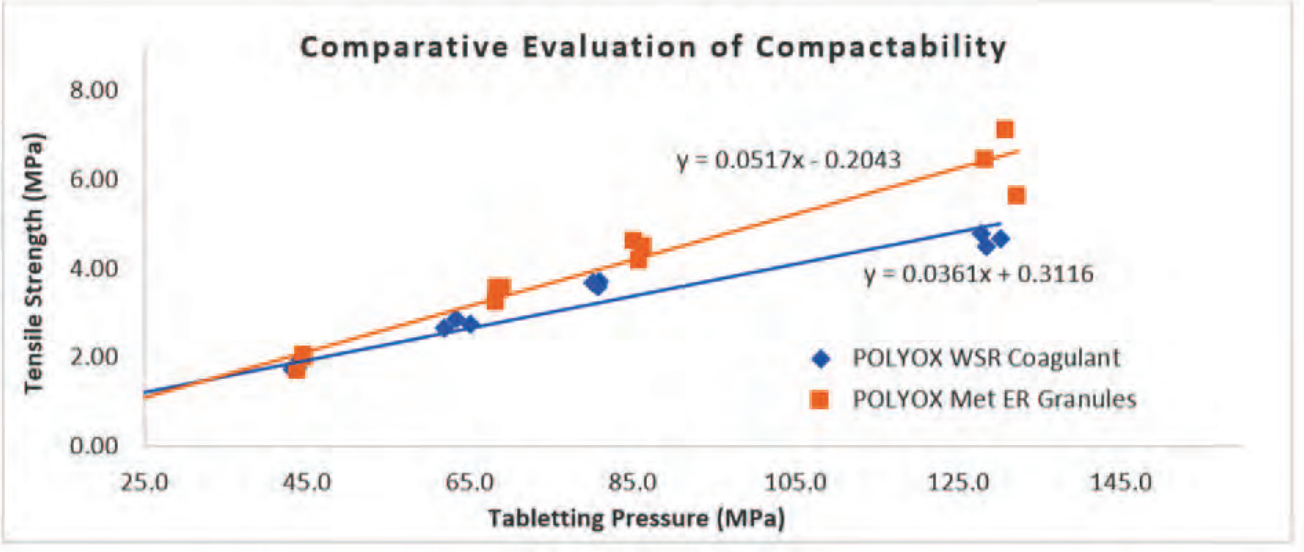
Researchers carried out the dissolution study as per Metformin Hydrochloride extended-release tablets monograph in USP. This clearly represents that the prototype with low-tablet weight complies with USP dissolution specification (3 hours-20% to 40%, 3 hours-45 % to 65% and 10 hours-NLT 85%).

An accelerated stability study (40°C/75% RH) showed consistent dissolution of the developed formulation over the study period (6 months), proving the stability of Metformin Hydrochloride extended-release tablets. In addition, the packaging material (aluminum pouch) of the drug product during the stability study might have helped to achieve the consistent drug release across the stability period.

Compaction Study

Researchers calculated the tensile strength for each tablet from obtained hardness, thickness, and diameter of the tablet, then plotted it against the compression pressure. The Metformin Hydrochloride extended-release granules were studied for compaction profile (Figure 2). The compaction slope observed for base polymer (POLYOX WSR Coagulant) was 0.036, and for Metformin Hydrochloride extended-release granules, it was 0.051. Data suggests the formed granules had better compactability compared to the base polymer. The change in compactability can be attributed to the proportion of API (~75% w/w) in the formulation.

FIGURE 2



Comparative Compaction Study

CONCLUSION

The primary advantage of top-spray granulation processes is ease of aqueous granulation with no rigorous milling process required because top-spray granulation provides a controlled granulation process. Fewer manufacturing steps means the process is easily adoptable to continuous manufacturing processes and leads to a cost- effective, better controlled process. The successful application of top-spray granulation led to the development of Metformin Hydrochloride extended-release tablets (500 mg) that were small and round, providing ease of dosing, as well as stable and consistent product dissolution.

Drug developers face several challenges when formulating lightweight tablets for extended release, maintaining a definite release rate being the main challenge. Low-weight tablets lead to better patient compliance, and this study demonstrated a cost-effective alternative with the same quality attributes of the finished product.

Overall, the study shows the application of POLYOX-based top-spray granulation to manufacturing smaller Metformin Hydrochloride extended-release tablets. By incorporating top-spray granulation into the manufacturing processes for extended-release tablets and formulating with patient needs in mind, formulators will equip the pharmaceutical industry with improved patient compliance and therapy outcomes, while reducing costs and increasing efficiency. ◆

REFERENCES

1. Formulation and Characterization of size reduced oral extended-release Metformin tablets, Asian Journal of Chemistry, 22 (3), 2442-2444, 2010
2. J H Flory and A I Mushlin, Effect of cost and formulation on persistence and adherence to Initial Metformin Therapy for type 2 diabetes, Diabetes Care, 43, e66- e67, 2020.
3. Manish Rane, Application of Polyethylene oxide in Hydrophilic Matrix Tablets, Pharma Times 45 (3) 41-48, 2013.
4. Metformin Hydrochloride Extended-Release Tablets, USP Pharmacopoeia, 2010.

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Technology & Services
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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. We can handle high potency compounds, solvents, flammables, and IR/SR/ER release profile products. Our sites deliver to more than 100 markets around the world, including the US/Canada, EU, Southeast Asia, Middle East, and South and Central Americas. All sites are TAA compliant. Our packaging lines are fully serialized. Our sites have over a 98% on-time delivery record! For more information, visit Bora Pharmaceuticals at **www.boracorpcdmo.com.**

Small Molecule CDMO

Cambrex is the leading small molecule company for drug substance, drug product, and analytical services across the entire drug lifecycle. With over 35 years' experience and more than 2,100 experts servicing global clients from sites in North America and Europe, Cambrex is a trusted partner in branded and generic markets for API and dosage form development and manufacturing. Cambrex offers an end-to-end partnership for the research, development, and manufacture of small molecule therapeutics along with a range of specialist drug substance technologies and capabilities, including biocatalysis, continuous flow, controlled substances, solid-state science, material characterization, and highly potent APIs. The team has expertise with conventional dosage forms, including oral solids, semi-solids, and liquids, as well as with manufacturing specialized dosage forms, such as modified-release, fixed-dose combination, pediatric, bi-layer tablets, stick packs, topicals, controlled substances, and sterile and non-sterile ointments. For more information, visit Cambrex at **www.cambrex.com.**

Technology & Services
SHOWCASE

CATALENT XPRESS PHARMACEUTICS™

Catalent Xpress Pharmaceutics™ is an integrated development solution to facilitate adaptive clinical trials and accelerate oral drugs through Phase 1 studies. By integrating formulation development, on-demand clinical manufacturing, regulatory support, and clinical testing, the approach can reduce both the cost and time taken to complete first-in-human trials. Xpress Pharmaceutics allows Catalent to work alongside innovator and clinical research organizations, and provide formulated clinical trial material in line with adaptive study protocols, providing a faster alternative to traditional clinical development models, and offering the advantage of flexible dose and/or formulation composition adjustment during a clinical trial, guided by real-time clinical data. For more information, contact Catalent Pharma Solutions at (888) SOLUTION or visit **www.catalent.com.**

DRUG DELIVERY PLATFORM

Celanese
The chemistry inside innovation™

Celanese Corporation is a global chemical leader in the production of differentiated chemistry solutions and specialty materials used in most major industries and consumer applications. With decades of experience in medical and pharmaceutical applications, our customers trust us to provide unrivaled service, world-class expertise, and quality that improve product development, enhance manufacturability, and elevate patient experiences. Our VitalDose® technology is a drug delivery platform providing controlled release through implant and insert dosage forms. Based in Dallas, Celanese employs approximately 8,500 employees worldwide and had 2021 net sales of $8.5 billion. For more information about solutions for the VitalDose sustained drug delivery platform, visit **vitaldose.com.**

DIFFERENTIATED INJECTABLE DELIVERY

Credence MedSystems is a medical technology company focused on delivering medications safely for the benefit of our patients, caregivers and partners. The Companion Safety Syringe System was born from Credence's core philosophy of *Innovation Without Change.* By providing passive safety and reuse prevention while using existing primary package components, the Companion offers best-in-class drug delivery with a vastly simplified path to market for our biotech and pharmaceutical partners. The Companion is available in luer needle, staked needle and dual chamber reconstitution configurations. In all cases, the user performs the injection, receives end-of-dose cues and then the needle automatically retracts into the syringe, which is then disabled. For more information, contact Credence MedSystems at 1-844-CMEDSYS, email info@credencemed.com, or visit **www.CredenceMed.com.**

CDMO

curia

Introducing Curia! Discover the end-to-end expertise of the CDMO formerly known as AMRI. What happens when the science of impact meets the art of possibility? A new era begins. The journey to breakthrough medicine is never simple. But the right CDMO partner can ease your path with scientific excellence, relentless curiosity, and expert, reliable delivery. For decades, Curia — formerly AMRI — has accelerated our partners' work, from research and development through commercial manufacturing. Together, we can turn life-changing potential into life-changing progress. For more information, visit Curia at **curiaglobal.com/curiosity.**

Technology & Services Showcase

Betadex Sulfobutyl Ether Sodium

CycloLab Cyclodextrin R&D Laboratory Ltd, Hungary has been operating in various fields of cyclodextrin-based research as well as pharma-grade cyclodextrin manufacturing for over 40 years. Our dedicated manufacturing facility produces betadex sulfobutyl ether sodium (SBECD under brand name Dexolve®) in multiple ton scale annually under cGMP conditions based on an FDA-approved Drug Master File. Dexolve is a potent API solubilizer and stabilizer excipient, already approved for various administration forms and marketed in 13 human and one veterinary formulation. Betadex sulfobutyl ether sodium has outstanding, favorable safety profile compared to non-complex forming solubilizing inactive ingredients such as surfactants. For more information, visit CycloLab Ltd. at **www.cyclolab.hu.**

Formulation Solutions

enteris BIOPHARMA
Intelligent Solutions for Oral Drug Delivery℠

Enteris BioPharma is a clinical-stage biopharmaceutical company offering innovative formulation solutions built around its proprietary oral drug delivery technologies. In addition to its formulation development expertise, Enteris BioPharma has a 32,000-sq-ft GMP facility in Boonton, NJ, offering an expanding range of manufacturing and development services for solid oral dosage forms, including handling and processing of highly potent APIs. The Peptelligence® and ProPerma® technologies provide oral bioavailability enhancement of challenging BCS-III and BCS-IV compounds by uniquely improving both permeation and solubility through a smart combination of pH-lowering, charge dispersal, membrane wetting, and solubilizing agents in a highly scalable solid oral dosage form. The technology has robust IP protection and extensive clinical validation. Enteris is the preferred partner for the oral delivery and development of peptides and small molecules. For more information, visit Enteris BioPharma at **www.enterisbiopharma.com.**

Hands-On Formulation Support

GATTEFOSSÉ

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

On-Body Drug Delivery

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

Technology & Services
SHOWCASE

FUNCTIONAL CHEMICALS

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

INJECTABLE DRUG DELIVERY

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.**

SPECIALIZED PRODUCTS & SERVICES

Pfanstiehl is a leading cGMP manufacturer of parenteral grade excipients and highly potent APIs. Pfanstiehl develops and manufactures high-purity, low-endotoxin (HPLE) carbohydrates such as trehalose, sucrose, mannitol, galactose, and mannose utilized as injectable excipients for the stabilization of proteins, mAbs, and vaccines. These HPLEs are also used as supplements for industrial cell culture, cell therapy, and cryopreservation media. Pfanstiehl also works closely with some of world's largest multinational pharmaceutical and biopharmaceutical firms, as well as with virtual pharmaceutical companies, to synthesize proprietary and commercial compounds in quantities ranging from grams to MT quantities. Manufacturing and development occur at Pfanstiehl's a 13-building campus located near Chicago, IL. For more information, visit us 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.**

October 2022 Advertiser Index

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Catalent Pharma Solutions	76	(888) 765-8846	www.catalent.com
Celanese	19	healthcare@celanese.com	www.healthcare.celanese.com
Credence MedSystems, Inc.	17	(844) 263-3797	www.CredenceMed.com
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