Drug Development & Delivery

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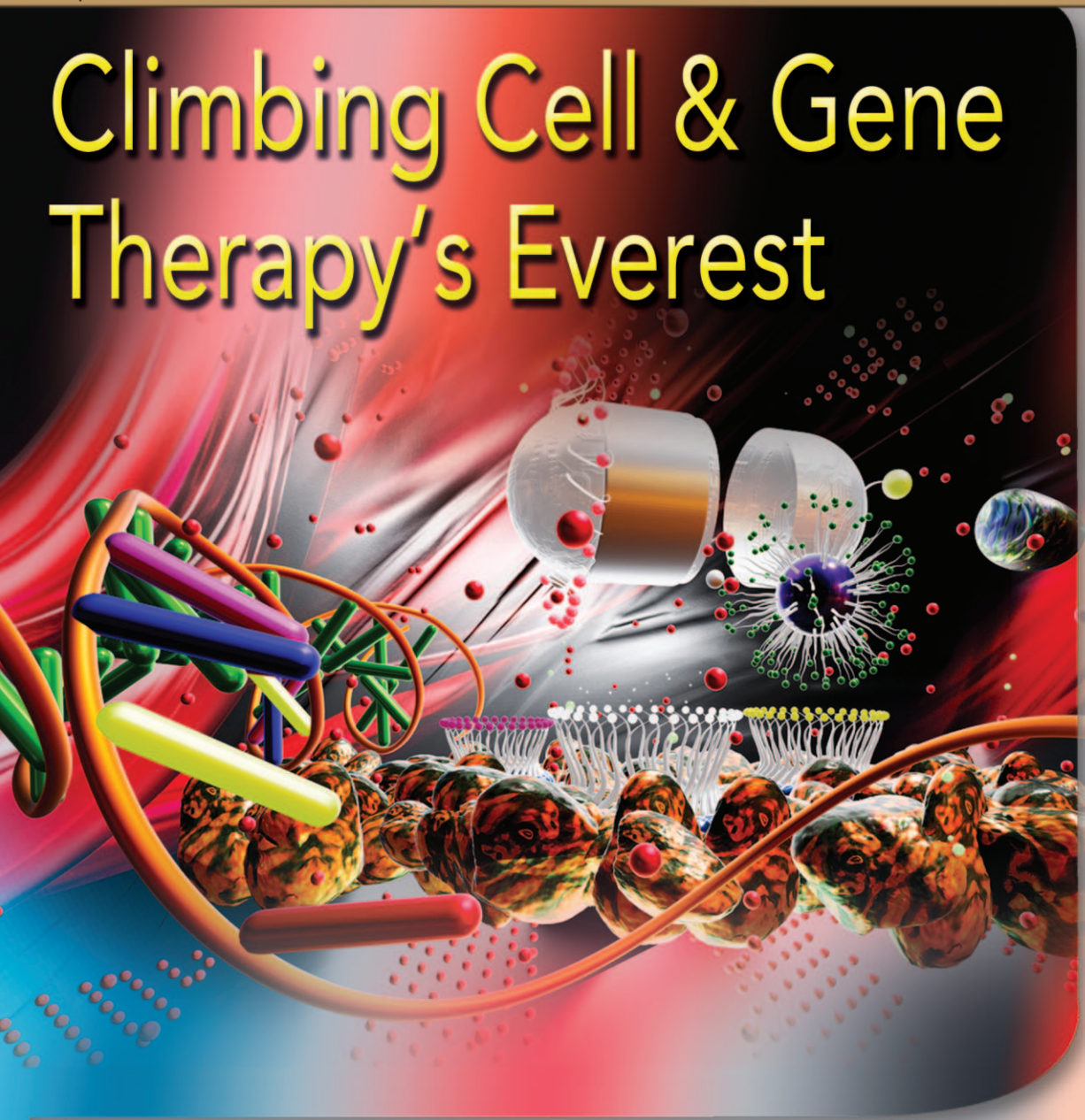
Climbing Cell & Gene Therapy's Everest



The Science & Business of Pharmaceutical and Biological Drug Development

IN THIS ISSUE

INTERVIEW WITH

SEVER PHARMA SOLUTIONS'

VP, TECHNOLOGY & SITE LEAD

TONY LISTRO

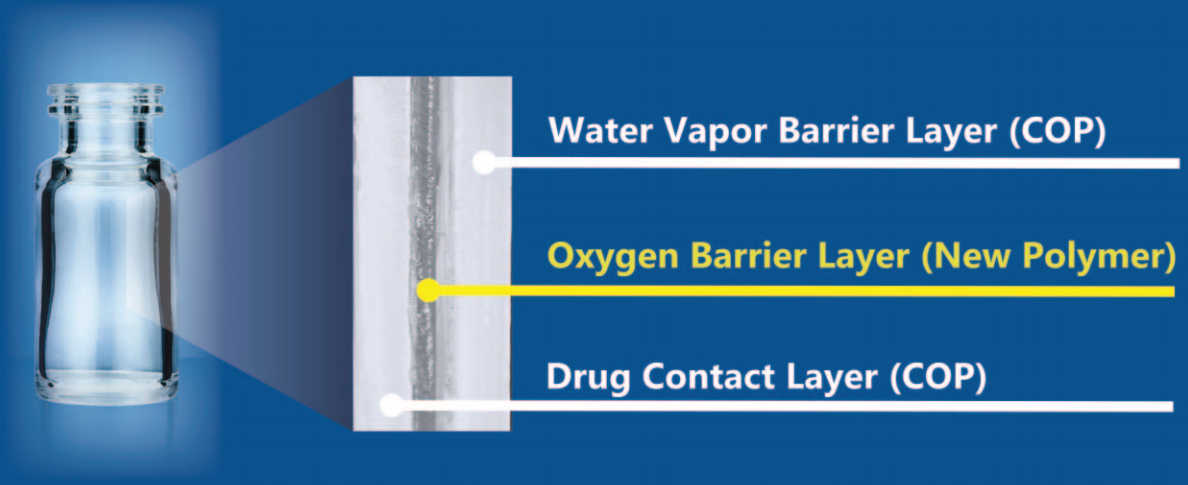
Cindy H. Dubin
Injection Devices: Designing in Sustainability, Usability & Digitization for Patient Compliance

Samir Acharya, PhD
Cell & Gene Therapy's Everest – The Challenges & Opportunities That Will Shape Success

Joseph Palumbo, MD
Effect of NE3107 on the Pharmacokinetics Profile of Carbidopa/Levodopa in Patients With Parkinson's Disease

OXYCAPT™ Multilayer Plastic Vial

Multilayer Structure



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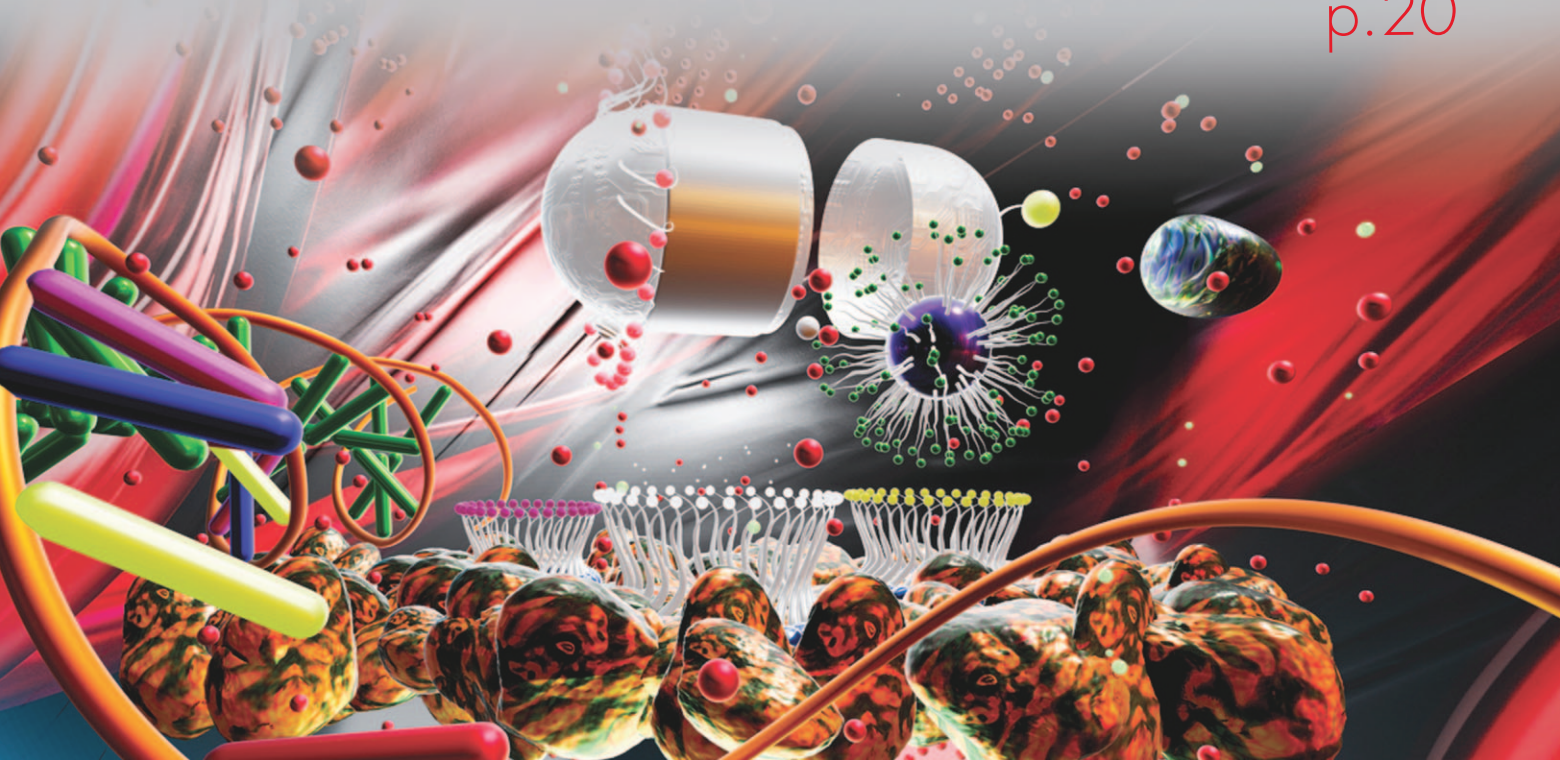
Owen Mumford
Pharmaceutical Services

Table of Contents

Cell & Gene Therapy's Everest

"The treatment potential of C&GTs is only just starting to be realized, and the increasing demand for treatments will help drive funding in the space. As the C&GT field evolves, it is becoming more critical than ever drug developers evolved convergently. This will require developers to embrace the transformative change within C&GT and the wider biopharma industry and be open to the key trends discussed within this article."

p.20



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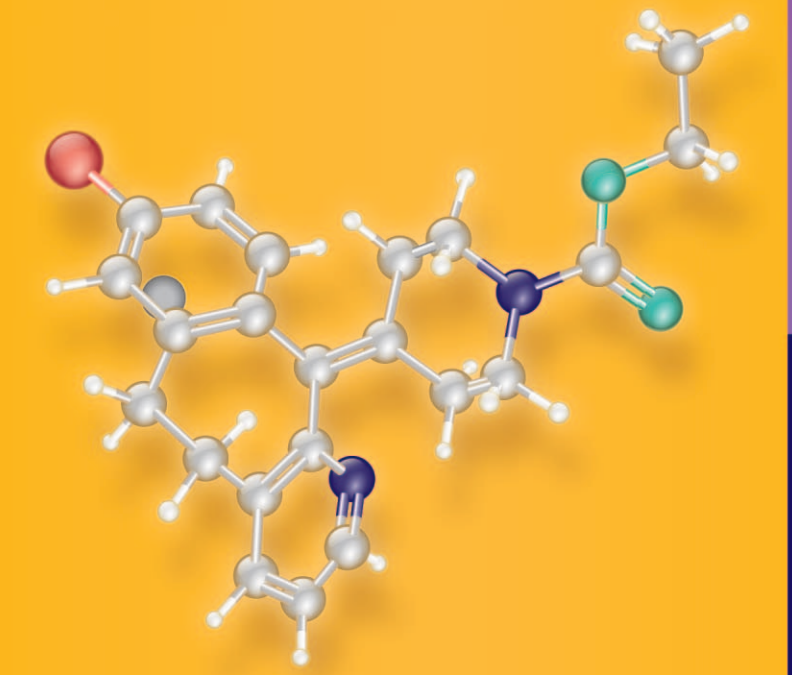

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Designing for Sustainability, Usability, & Digitization

"The global injectable drug delivery market could reach $1.317 billion by 2030, fueled by the prevalence of life-threatening diseases, the development of smart wearable devices, and the Internet of Things (IoT), which makes it possible to collect valuable data directly from injection devices. Prefilled syringes, autoinjectors, and pen injectors are all expected to become more popular as pharma companies seek alternatives to oral dosage regimens and deliver long-acting drugs in an effort to improve patient compliance. Drug and device developers do face a bit of an uphill battle as they tackle challenges related to delivering viscous and large-volume biologics, preserving the integrity of sensitive formulations, regulatory issues, and manufacturing scalability."

p.46

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Cellares Announces Bristol Myers Squibb has Joined Technology Adoption Partnership Program to Evaluate Automated Manufacturing of CAR-T Cell Therapy on the Cell Shuttle Platform

Cellares, the first Integrated Development and Manufacturing Organization (IDMO) dedicated to clinical and industrial-scale cell therapy manufacturing, recently announced global biopharmaceutical company and cell therapy developer Bristol Myers Squibb has joined its Technology Adoption Partnership (TAP) program. As part of the agreement, the pharma leader will enter into a proof-of-concept transfer process for the manufacture of one of its CAR-T cell therapies, using Cellares' automated manufacturing platform, the Cell Shuttle.

Cellares' TAP program is a fast and low-risk opportunity for cell therapy developers to adopt the company's automated manufacturing technology for products in their pipeline. Bristol Myers Squibb is leveraging this program to evaluate the automated manufacturing process and produce comparability data confirming the Cell Shuttle as a viable, cost-efficient, and scalable manufacturing solution for cell therapies. Through its TAP program, Cellares is working with leading cell therapy developers to implement the Cell Shuttle as a clinical and commercial-stage GMP manufacturing solution at its IDMO Smart Factories.

"We're pleased to welcome Bristol Myers Squibb to the TAP program, and we look forward to demonstrating the ease and efficacy of transferring one of BMS's cell therapy process onto the Cell Shuttle in the months to come," said Cellares CEO Fabian Gerlinghaus. "By combining integrated automation with a high-throughput platform, the Cell Shuttle offers unrivaled scalability for the cell therapy industry, while improving quality and lowering COGS."

Cellares' flexible manufacturing technology supports both autologous and allogeneic cell therapy processes and approximately 90% of cell therapy modalities. Manual processes can be automated and tech-transferred onto Cellares' automated Cell Shuttle platform in only six months via the company's Technology Adoption Partnership (TAP) program. Under the TAP program, participating cell therapy developers can tech-transfer their cell therapy processes onto a Cell Shuttle at any stage – during pre-clinical development, in the clinic, or after regulatory approval. Thanks to automation, standardization, and software-defined manufacturing (SDM), every tech transfer thereafter is instantaneous, to any other Cell Shuttle in any other IDMO Smart Factory anywhere in the world.

Cellares is the first Integrated Development and Manufacturing Organization (IDMO) and takes an Industry 4.0 approach to mass manufacturing the living drugs of the 21st century. The company is both developing and operating integrated technologies for cell therapy manufacturing to accelerate access to life-saving cell therapies. The company's Cell Shuttle integrates all the technologies required for the entire manufacturing process in a flexible and high-throughput platform that delivers true walk-away, end-to-end automation. Cell Shuttles will be deployed in Cellares' Smart Factories around the world to meet total patient demand for cell therapies at global scale. Partnering with Cellares enables academics, biotechs, and pharma companies to accelerate drug development and scale out manufacturing, lower process failure rates, lower manufacturing costs, and meet global patient demand.

The company is headquartered in South San Francisco, CA, with its commercial-scale IDMO Smart Factory in Bridgewater, NJ. The company is backed by world-class investors and has raised over $355 million in financing.

Bio-Rad Launches First StarBright Red Dye & Extends Range of Antibody Markers Conjugated to StarBright Dyes to Enhance Multiplex Flow Cytometry & Research Capabilities

Bio-Rad Laboratories, Inc. recently announced the launch of the 29th StarBright Dye, StarBright Red 670, and an expansion of its current range with 29 additional highly validated antibodies conjugated to StarBright Blue 700 and StarBright Violet 610 Dyes. Including additional human and mouse targets and introducing dog, cow, and pig targets, the new range provides greater choice and flexibility in conventional and full-spectrum multicolor flow cytometry panels, expanding research capabilities across veterinary immunology research.

Offering exceptional brightness with narrow excitation and emission profiles for precise resolution, Bio-Rad's line of StarBright Dyes provides researchers with validated flow antibodies against key immunology targets conjugated to proprietary fluorescent nanoparticles. StarBright Dyes are compatible with the Bio-Rad ZE5 Cell Analyzer and S3e Cell Sorter, as well as most flow cytometers and experimental protocols, without the need for special buffers. Minimal lot-to-lot variation ensures reproducible and consistent staining, and the dyes are resistant to photobleaching with no loss of signal in fixation. The additional 29 antibody markers will soon be available on all StarBright Dyes.

"Now totaling 29 dyes for the 355, 405, 488, 561, and 640 nm lasers, the Bio-Rad StarBright Dye range is currently the largest series of dyes for conventional and full spectrum flow cytometry," said Mike Blundell, PhD, Product Manager, Flow Cytometry, Life Science Group, Bio-Rad. "By extending our existing portfolio of 35 antibody markers to include another 29 human, mouse, and now cow, dog, and pig targets, we can offer our customers greater flexibility and choice when designing multicolor flow cytometry panels, including for translational and immunological research in veterinary species."

Bio-Rad Laboratories, Inc. (NYSE: BIO and BIOb) is a leader in developing, manufacturing, and marketing a broad range of products for the life science research and clinical diagnostics markets. Based in Hercules, CA, Bio-Rad operates a global network of research, development, manufacturing, and sales operations with over 8,200 employees and $2.8 billion in revenues in 2022. Our customers include universities, research institutions, hospitals, food safety and environmental quality laboratories, and biopharmaceutical companies. Together, we develop innovative, high-quality products that advance science and save lives. For more information, visit bio-rad.com.

Foundery Launches Inaugural Biotech Venture Creation Fund to Accelerate the Development of Novel Immunotherapies

Foundery recently announced an initial closing of its inaugural fund, Foundery I, LP, with total capital commitments and contributed assets as of the closing equal to $29.6 million. Founded in 2021 by science-first industry leaders Max Krummel, PhD, Michel Streuli, PhD, and Venkataraman "Sriram", PhD, Foundery seeks to validate early stage immunotherapy programs in collaboration with university researchers and their institutions.

"Foundery is pleased to launch this new fund with the support of our limited partners who share in our belief that by fostering integrated early-stage drug development collaborations with university investigators, we can accelerate the cost-effective creation of novel immunotherapies that hold the potential to transform lives," said Dr. Krummel. "Together, we are setting a new standard for mutually beneficial and efficient collaborations."

Foundery is committed to driving progress by actively collaborating with researchers and clinicians who share a passion for pioneering the future of immunotherapy. The Foundery Immune Studio, located adjacent to the University of California, San Francisco (UCSF) Parnassus campus, empowers faculty to translate their scientific breakthroughs into impactful therapies via close collaboration with Foundery's drug development team. Foundery's master agreements with UCSF and the University of Arizona provide a highly streamlined path for principal investigators and Foundery to partner. Foundery manages a fully functioning state-of-the-art lab and internal discovery team to evaluate and validate first-in-class drug target candidates and develops Investigational New Drug (IND)-enabling drug packages that can be out-licensed or used as the foundation for venture creation.

"Led by a founding team of accomplished drug pickers, Foundery offers a capital-efficient investing approach that significantly de-risks the preclinical drug development process," said Srini Akkaraju, MD, PhD, Founder and Managing General Partner at Samsara BioCapital and Limited Partner in Foundery Fund I. "Foundery is also poised to redefine venture creation in partnership with academic institutions and realize the incredible opportunities that exist at research universities to address high unmet-need diseases."

"Foundery is opening up a new frontier in biotech investing," added Jeff Brody, Managing Director emeritus and Co-founder, Redpoint Ventures, another Foundery Fund I Limited Partner. "Foundery's Immune Studio offers a groundbreaking investment model that employs a reusable preclinical R&D team that can conduct target validation and proof-of-concept testing, iteratively across dozens of programs, to help academics and their institutions de-risk their discoveries and hold on to a larger percentage of the upside."

Foundery Fund I currently has nine preclinical programs in its pipeline across autoimmunity, inflammation, and oncology therapeutic areas, including two early stage "platform" programs that aim to tackle historically challenging therapeutic targets. Foundery anticipates initiating business development activities for its pre-IND drug development candidates as early as the second half of 2024.

Limited Partners in Foundery Fund I include an established family office, a public research university endowment, and growth and impact-oriented high-net worth individuals.

Recipharm & Honeywell to Speed Development of Inhalers With Near-Zero Global Warming Potential Propellant

Recipharm and Honeywell recently announced a commercial partnership that will speed the development of pressurized metered dose inhalers (pMDIs) that use Honeywell's near-zero global warming potential (GWP) propellant.

As many as 384 million people globally suffer from chronic obstructive pulmonary disease (COPD), and about 262 million people suffer from asthma. Many of these patients are treated using pMDIs that have a high global warming potential due to the use of hydrofluoroalkanes (HFAs) as propellants.

Honeywell Solstice Air (HFO-1234ze(E) cGMP) is a hydrofluoroolefin (HFO) propellant in clinical development today for pMDIs that has 99.9% less global warming potential than HFAs. In addition, Honeywell Solstice Air is non-flammable, non-ozone-depleting and volatile organic compound (VOC)-exempt under federal and state guidelines.

"Honeywell is making great strides to offer patients who rely on pMDIs a lower greenhouse gas solution to meet their medical needs," said Laura Reinhard, Vice President and General Manager, Honeywell Foam and Industrial Products. "Through our collaboration with Recipharm, the increased use of near-zero GWP propellant used in pMDIs will help reduce the environmental impact of the life-saving medical treatments patients need, without sacrificing performance."

"As the first CDMO to partner with Honeywell for use of Solstice Air, this collaboration significantly accelerates and simplifies our customers' pathway to develop the next generation of low greenhouse gas pMDIs," said Chris Hirst, president of Recipharm's Advanced Delivery Systems business unit. "Our collaboration is supported by Recipharm's investment in manufacturing with HFO-1234ze(E) cGMP at our Holmes Chapel, United Kingdom site, and the further development of the Bespak valve range to ensure the required product performance."

The partnership with Honeywell follows Recipharm's announcement that it is expanding its pMDI product development and manufacturing capabilities to accommodate increased demand from pharmaceutical companies. Research will be conducted at Recipharm's dedicated inhalation development facility in Research Triangle Park, NC. Recipharm customers will also benefit from the company's market-leading Bespak valves, which have been optimized to ensure performance with products containing Honeywell Solstice Air as the propellant.

Honeywell has invested more than $1 billion in research, development, and new capacity for its Solstice technology, which has applications in refrigerants, blowing agents, aerosols and solvents. Use of Honeywell Solstice technology has helped avoid the potential release of the equivalent of more than 326 million metric tons of carbon dioxide into the atmosphere, equal to the carbon emissions from nearly 70 million gasoline-powered passenger vehicles per year.

Honeywell is committed to achieving carbon neutrality in its operations and facilities by 2035. About 60% of Honeywell's 2022 new product introduction research and development investment was directed toward Environment, Social and Governance (ESG) oriented outcomes for customers.

As a CDMO focusing on sustainability, Recipharm is committed to the Science Based Targets initiative (SBTi). It has set ambitious and transparent targets to reduce its emissions from direct operations by 42% and emissions from the full value-chain by 25% by 2030. It also has B- rating for Climate from CDP which indicates Recipharm is showing clear evidence of managing its climate impact.

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Tiziana Life Sciences Announces FDA IND Clearance of Intranasal Foralumab for the Treatment of Alzheimer's Disease

Tiziana Life Sciences Ltd. recently announced the US FDA has cleared the Investigational New Drug (IND) application for intranasal foralumab to be studied in Alzheimer's disease. Foralumab could be a potentially groundbreaking treatment for Alzheimer's disease, given it targets the disease's underlying pathology by addressing the resulting neuroinflammation caused by the accumulation of toxic proteins in the brain.

Gabriele Cerrone, Chairman, acting CEO, and founder of Tiziana Life Sciences, said "The IND clearance is a significant milestone for Tiziana that highlights the strength and the therapeutic potential of foralumab. We are deeply committed to advancing the field of neurodegenerative diseases and bringing much-needed relief to patients suffering from Alzheimer's with a novel therapeutic approach. We are thrilled to have reached this critical juncture and are eager to move forward with the necessary trials to evaluate the effectiveness of foralumab in Alzheimer's disease in combination with an FDA approved therapy or as a single agent."

Professor Howard L. Weiner, the Robert L. Kroc Professor of Neurology at the Harvard Medical School, Director and Founder of the Partners Multiple Sclerosis Center and Co-Director of the Center for Neurologic Diseases at Brigham and Women's Hospital, a founding member of Mass General Brigham Healthcare System, added "The IND clearance is a significant step forward in the fight against Alzheimer's disease. Foralumab shows great promise in targeting the pathological hallmarks of the disease, and I am optimistic about its potential to offer a breakthrough treatment option for patients suffering from this devastating condition. I look forward to witnessing the progress of this important therapy."

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

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

BioCorRx Submits Expanded Access Treatment Protocol to FDA for Implantable Biodegradable Naltrexone Pellet for Opioid Use Disorder Treatment

BioCorRx Inc. recently announced its submission to the US FDA of an expanded access program application for BICX104 (implantable naltrexone pellet) for the treatment of opioid use disorder (OUD) patients that meet program eligibility criteria.

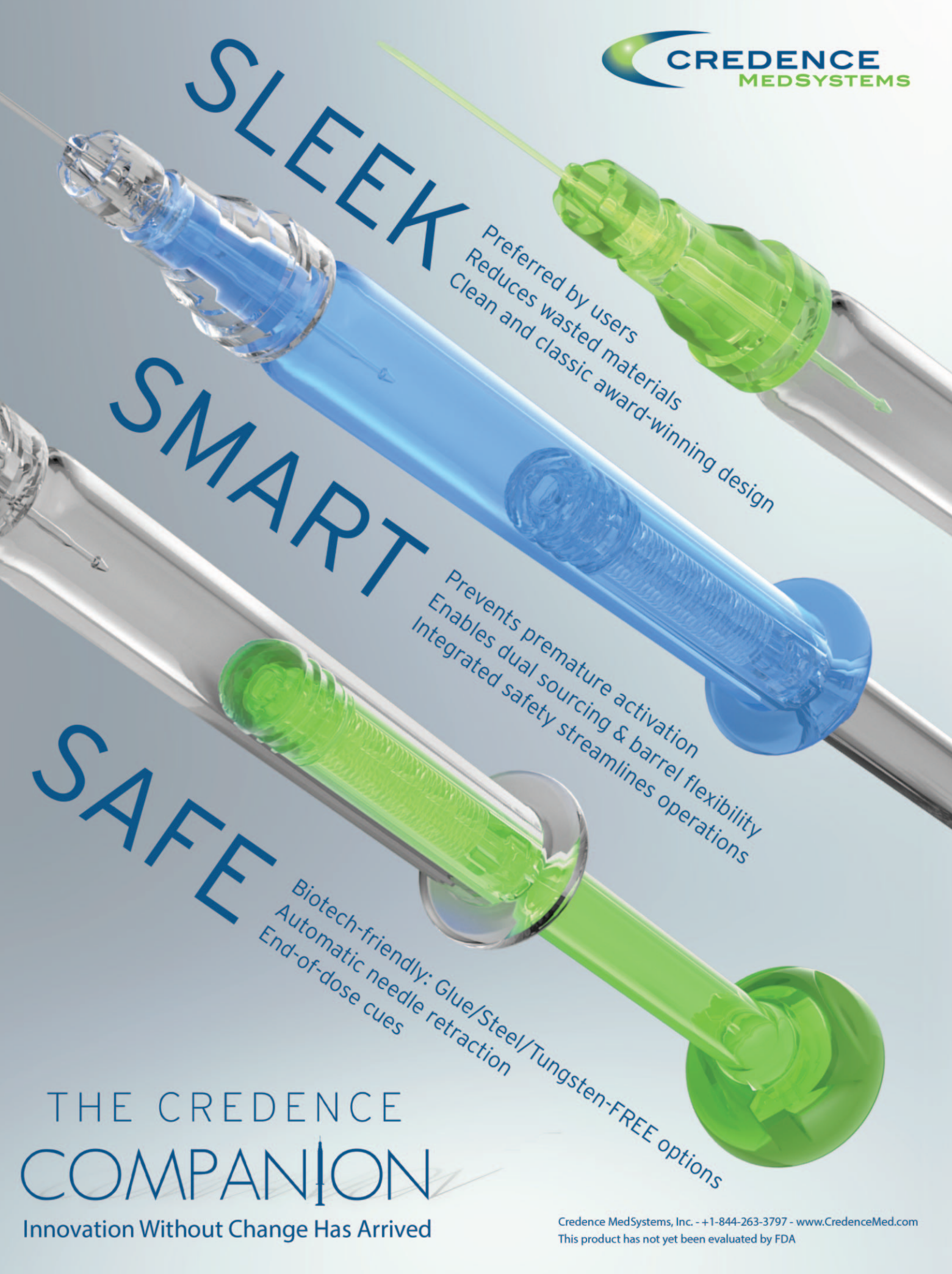
Brady Granier, President of BioCorRx, Inc., and CEO of BioCorRx Pharmaceuticals, Inc., said "We chose to submit this expanded access treatment protocol to bring the benefits of our safe, effective, and potentially life-saving naltrexone implant to patients suffering with OUD. Our Phase 1 clinical trial results encouraged us to apply to the FDA to get our BICX104 treatment to the public as soon as possible. If our expanded access application is approved, we look forward to implementing our program to promote the distribution of BICX104 to OUD patients through qualified healthcare providers. Per FDA guidance, we expect to know if we can proceed in doing so in 30 days. In the meantime, we continue to work on fulfilling the requirements needed for our New Drug Application (NDA) for full FDA marketing approval. BioCorRx is committed, through both today's expanded access filing and our Fast Track application announced July 18, 2023, to meeting our corporate goals of not only getting BICX104 clinical trials promptly completed and obtaining full FDA approval of our product, but also to help those in need now."

Expanded access (also known as "compassionate use") is an FDA program that allows drug companies to provide access to an investigational medical product before full FDA approval to patients with a serious or immediately life-threatening disease or condition where standard treatment options have been exhausted or are not suitable. Data published on the FDA website indicates a 98.4% approval rate (62 out of 63) for expanded access applications submitted to the Center for Drug Evaluation and Research (CDER) for treatment protocols between 2018 and 2022.

BICX104, which is being developed by BioCorRx Pharmaceuticals, Inc., the company's controlled clinical-stage pharmaceutical subsidiary, is a biodegradable, long-acting subcutaneous pellet of naltrexone for the treatment of OUD being developed with the goal of improving patient compliance to naltrexone therapy compared to other marketed treatments. The BICX104 clinical study was a Phase 1, open-label, single-center study in two parallel groups of randomized healthy volunteers to evaluate the PK and safety of BICX104 implantable subcutaneous naltrexone pellets and the marketed once-a-month intramuscular depot naltrexone injection, Vivitrol.

BICX104 is being developed through a cooperative agreement with the NIDA, part of NIH, under award number UH3DA047925, funded by the Helping to End Addiction Long-term Initiative or NIH HEAL Initiative. This award is subject to the Cooperative Agreement Terms and Conditions of Award as set forth in RFA DA-19-002, titled Development of Medications to Prevent and Treat Opioid Use Disorders and Overdose (UG3/UH3) (Clinical Trial Optional).

The NIH Helping to End Addiction Long-term Initiative or NIH HEAL Initiative, is an aggressive, trans-NIH effort to speed scientific solutions to stem the national opioid public health crisis. Launched in April 2018, the initiative is focused on improving prevention and treatment strategies for opioid misuse and addiction and enhancing pain management.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Ocean Biomedical Announces New Patent for Anti-Fibrosis Discovery With Allowance in Alcoholic Liver Disease & Multiple Fibrotic Conditions

Ocean Biomedical, Inc. recently announced the United States Patent and Trademark Office has issued a patent covering Ocean's anti-Chitinase 1 small molecule candidate.

Dr. Jack A. Elias, MD, one of Ocean's Scientific Co-founders, discovered this molecule to be a key factor in controlling and inhibiting fibrosis progression, with potential application in several major fibrotic diseases. Targeted diseases include alcoholic liver disease, idiopathic pulmonary fibrosis (IPF), scleroderma, nonalcoholic steatohepatitis (NASH), and Hermansky-Pudlak Syndrome (HPS), a rare disease that currently has no known treatments. Ocean Biomedical is the exclusive licensee of this patent family.

Ocean's approach has shown an 85%-90% reduction in collagen accumulation in four different IPF and HPS pulmonary fibrosis animal models. This treatment approach is anticipated to be well-tolerated in humans based on data from original (non-Ocean) clinical studies and recent EPA data. In addition to the targeted diseases noted above, the patent notes potential use in conditions of chemotherapy-induced pulmonary fibrosis, scleroderma, collagen vascular disease, lupus, rheumatoid arthritis, and interstitial lung disease associated with asbestosis, silicosis, and grain exposure. Nearly all these fibrotic conditions currently lack adequate treatments.

The patent is U.S. Patent No. 11,717,528 B2 is titled Methods and Compositions Relating to the Treatment of Fibrosis.

IPF degrades the respiratory system. It is characterized by progressive scarring of the lung tissues, leading to irreversible and often rapid decline in lung function. Estimates of IPF prevalence indicate that over 150,000 people suffer from IPF in the US along with over 50,000 people in Europe. There are currently only two approved drugs for treating IPF, both of which have limited efficacy. Current therapies slow the deterioration of lung function but with significant side effects. IPF is a disease with a major unmet need for curative therapeutics.

HPS is an ultra-rare disease that has an estimated worldwide prevalence of 1 to 9 in 1,000,000 people, though prevalence can vary by subtype and region. For example, HPS-1 affects approximately 1 in 1,800 people in northwestern Puerto Rico. Most patients with HPS develop lung fibrosis that progresses rapidly and is typically lethal within ten years of diagnosis. No therapeutic interventions are currently approved by the FDA for the treatment of HPS, and lung transplantation remains the only potentially life-prolonging treatment.

"We desperately need more treatment options for patients with pulmonary fibrosis," said Dr. Elias, former Dean of Medicine and Biological Science at Brown University. "I'm hopeful we can develop these discoveries into a new, more effective treatment approach for patients and doctors."

"Ocean Biomedical is committed to advancing novel discoveries that have the potential to treat global unmet needs," added Elizabeth Ng, Chief Executive Officer of Ocean Biomedical.

"Combining innovative science with a strong management team has potential for great impact," said Dr. Chirinjeev Kathuria, Ocean Biomedical's co-founder and Executive Chairman. "We are pleased to receive this patent and look forward to moving these important drug candidates into clinical trials as soon as possible."

US FDA Approves Orphan Drug Designation for NXC-201 as a Treatment for Multiple Myeloma

Nexcella, Inc. recently announced the US FDA has granted Orphan Drug Designation (ODD) designation for NXC-201 for the treatment of a life-threatening form of blood cancer, multiple myeloma. NXC-201, a next-generation CAR-T cell therapy, is currently being evaluated in a Phase 1b/2a clinical trial NEXICART-1 (NCT04720313).

The FDA's Office of Orphan Products Development grants orphan designation status to drugs and biologics that are intended for the safe and effective treatment, diagnosis or prevention of rare diseases, or conditions that affect fewer than 200,000 people in the US. Orphan Drug Designation provides certain benefits, including financial incentives, to support clinical development and the potential for up to 7 years of market exclusivity in the US upon regulatory approval.

"We are pleased to receive FDA's orphan drug designation in multiple myeloma for NXC-201, the only clinical-stage BCMA-targeted CAR-T cell therapy with no neurotoxicity observed in over 50 patients dosed to date," said Ilya Rachman, MD, PhD, Executive Chairman of Nexcella. "We are thrilled to potentially expand therapeutic options for multiple myeloma patients, while eliminating the most feared adverse effect of this therapeutic class, neurotoxicity."

Gabriel Morris, President of Nexcella, added "Orphan drug designation for NXC-201 represents a substantial value creating step along our path to unlocking planned wide adoption of CAR-T technology by transitioning it to an outpatient domain."

Multiple myeloma (MM) is an incurable blood cancer of plasma cells that starts in the bone marrow and is characterized by an excessive proliferation of these cells. Despite initial remission, unfortunately, most patients are likely to relapse. There are 35,730 patients in the United States diagnosed with MM each year. Prognosis for patients who do not respond to or relapse after treatment with standard therapies, including protease inhibitors and immunomodulatory agents, remains poor. The $13.9 billion Multiple Myeloma market in 2017 is expected to reach $28.7 billion in 2027 according to Wilcock, et al. Nature Reviews.

Nexcella, Inc. is a Los Angeles, CA-based clinical-stage biopharmaceutical company engaged in the discovery and development of novel cell therapies for oncology and other indications. Our lead candidate, next generation BCMA-targeted CAR-T NXC-201 for relapsed/refractory multiple myeloma and relapsed/refractory AL amyloidosis has produced 92% and 100% response rates in each indication, respectively, as of February 9, 2023 across 58 patients. We believe NXC-201 has potential to be the world's first outpatient CAR-T. Our N-GENIUS platform allows us to discover, develop, and manufacture cutting-edge cell therapies for patients in need.

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Phathom Pharmaceuticals Announces Submission of 6-Month Stability Data in Support of Erosive GERD NDA

Phathom Pharmaceuticals, Inc. recently announced it has submitted to the FDA 6-month stability data from its long-term and accelerated stability program for its reformulated vonoprazan tablets. The additional stability was required for the FDA to complete its NDA review for vonoprazan, a novel first-in-class potassium-competitive acid blocker (PCAB), for the treatment of Erosive GERD (gastroesophageal reflux disease), also referred to as erosive esophagitis.

With the submission of these data, Phathom has satisfied the FDA's request for additional data in response to the Complete Response Letter (CRL) issued in February 2023 relating to specifications and controls for a nitrosamine drug substance related impurity, N-nitroso-vonoprazan (NVP). Phathom resubmitted the NDA for vonoprazan for Erosive GERD in May 2023 on the basis of 3 months of stability data and was assigned a PDUFA goal date of November 17, 2023.

"We are happy to share that the 6-month stability data continue to demonstrate effective control of NVP, which is another big step forward as we prepare for a planned launch in the fourth quarter of this year," said Terrie Curran, President and Chief Executive Officer of Phathom. "The latest stability data confirm that our minor product reformulation has limited the presence of NVP, and we believe these data comfortably support the proposed shelf-life for vonoprazan tablets. We look forward to working with the FDA as it completes its review."

The long-term and accelerated 6-month data from Phathom's stability program have demonstrated that the minor drug product tablet reformulation is controlling NVP growth through 6 months and keeping levels greater than tenfold below the acceptable daily intake limit of 96 ng/day or 2.4 ppm based on the maximum approved daily dose of 40 mg/day.

The NDA seeks regulatory approval for vonoprazan as a treatment for the healing and maintenance of healing of Erosive GERD, and relief of associated heartburn symptoms, and was previously classified as a Class 2 resubmission with a 6-month review period. If approved, a combined US commercial launch for Erosive GERD and H. pylori is planned for the fourth quarter of 2023.

Phathom Pharmaceuticals is a biopharmaceutical company focused on the development and commercialization of novel treatments for gastrointestinal diseases. Phathom has in-licensed the exclusive rights in the US, Europe, and Canada to vonoprazan, a first-in-class potassium-competitive acid blocker (PCAB).

Mitsubishi Gas Chemical Develops First-Ever, PFAS-Free Oxygen Absorber to Help the Industry Meet Emerging Global Regulations

In response to the growing legislation around per- and polyfluoroalkyl substances (PFAS), Mitsubishi Gas Chemical (MGC) has launched the first future-proof, eco-friendly packaging solution for the industry using a cleaner chemistry within record-breaking turnaround. MGC will be debuting the PFAS-free AGELESS oxygen absorber technology at PACK EXPO Las Vegas, Sept. 11-13 in booth SU-7490.

PFAS, known as "forever chemicals," have been widely used in industry and consumer products worldwide since the mid-20th century. Once favored for their oil and water-resistant properties, PFAS has recently been under public scrutiny for its inability to breakdown in the environment and potential adverse health effects. As a result, legislators around the world have enacted laws banning PFAS in products, including packaging, putting pressure on manufacturers across a wide spectrum of industries for coordinated action now.

As science around PFAS improves to better identify data gaps and understand end-of-life concerns, stakeholders are presented with an incredibly broad definition of PFAS across governments, making the regulatory landscape even more difficult to navigate. MGC has revolutionized its oxygen absorber technology by eliminating PFAS and replacing it with an advanced proprietary formula to meet new stringent global regulations. This game-changing innovation is preceded by more than 40 years of proven AGELESS technology, MGC's well known and established brand, now reengineered to support the industry's progress towards ambitious sustainability goals.

By completely removing a toxic grease-proofing agent from its oxygen absorber, MGC is introducing a first-of-its-kind, universal packaging solution that is 100 percent PFAS-free but doesn't compromise quality, performance, and safety. PFAS-free AGELESS oxygen absorbers are oil-resistant and can deoxidize the interior of sealed packages to maintain flavor, color, fragrance, and nutrition of freshly prepared food as well as dramatically extend shelf life.

As pioneers of the world's first oxygen absorber, MGC brings the history, technical know-how and reliability that customers expect, paired with future-forward thinking the industry needs. PFAS-free AGELESS can create a 99.9% oxygen-free package within 24 hours, which keeps a variety of foods fresh without the use of unhealthy preservatives – drastically extending product shelf life, reducing waste, and improving product quality.

"To develop a brand new, PFAS-free solution for our customers within such a short stretch of time is a truly herculean feat," said Sean Hael, Sales and Marketing General Manager at Mitsubishi Gas Chemical America. "PFAS-free AGELESS supports companies advancement towards long-term sustainability goals, complies with evolving regulations, all while providing the same performance and efficacy that our customers know and trust."

PFAS-free AGELESS is used to protect and preserve a variety of products, including processed meats, meat snacks, baked goods, dried fruits, coffee, pet treats, pharmaceuticals, and nutraceuticals.

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CELL & GENE THERAPY

Cell & Gene Therapy's Everest – The Challenges & Opportunities That Will Shape Success

By: Samir Acharya, PhD, Rajiv Vaidya, PhD, Laura Kerepesi, PhD, and Cyrill Kellerhals, MBA

INTRODUCTION

Cell and gene therapies (C&GTs) are a rapidly evolving aspect of the biopharma industry, playing a significant role in shaping the future of healthcare and the treatment of genetic diseases. Despite the progress made in recent years, there are still many challenges and trends that must be addressed for C&GT to become a viable and widely used treatment option.

The following shares insights on the current challenges and trends in the field of C&GT, exploring the current and future challenges facing C&GTs developers and manufacturers and how to overcome them.

VIRAL VECTORS AS CELL AND GENE THERAPY TOOLS

Research and development has rapidly evolved into the fast-paced and competitive C&GT industry. Advances in gene-altering capabilities have played a big role in this evolution. Viral vectors are used regularly in C&GTs as they are excellent at delivering payloads into cells for genetic modification.

The viral vector and plasmid DNA market is expected to rise from $0.69 billion in 2021 to $1.38 billion in 2026, at a compound annual growth rate (CAGR) of 14.8%.[1] Growth of the viral vector and plasmid DNA market is extremely important to the ongoing success of C&GTs, with many of these therapies using viral vectors as part of their mode of action.

The continued success of C&GTs relies upon continued advances to improve the safety and efficacy of these treatments. Further transformative change in C&GTs is likely to come from trends

in process development, technology requirements, and quality requirements. These are three areas in which challenges are rife, and overcoming these challenges offers opportunities to create commercially viable and effective therapeutics.

UNDERSTANDING THE CHALLENGES IN PROCESS DEVELOPMENT

Process development is critical to the optimization and scaling of C&GT manufacturing processes as it enables the production of consistent and high-quality therapeutics. Although process development is vital, there are many challenges associated with it, and a future trend in the C&GT space will be to address them.

The biopharma industry is experiencing a growing demand for viral vectors, such as adeno-associated viruses (AAVs), and there is an expectation that these vectors meet high standards of quality, yield, and potency.

Quality should be the primary focus during the process development stage as it ensures the final product meets the neces-

sary standards. Incorporating quality-by-design (QbD) into the process development can help accelerate timelines, cut costs, and establish dependable and robust manufacturing processes. QbD is a process concept in which product features are created and designed in response to customer requirements. Working with robust and reliable QbD processes takes advantage of the interwoven nature of timelines and budgets to streamline operations and reduce costs.

ADAPTING TO TECHNOLOGICAL ADVANCEMENTS

In viral vector manufacturing, ensuring effective process development requires the adoption of new and improved technologies. As these new technologies are developed, it becomes increasingly challenging to adapt and integrate them into existing processes.

Traditionally, ultracentrifugation (UF) was considered the gold standard method for removing empty vector capsids from viral vectors, which is vital for the final product's efficacy and safety. Despite its effectiveness, UF is an open process and therefore has a higher risk of contamination than closed-process alternatives. As the industry shifts toward larger-scale production using suspension or adherent platforms, regulators are encouraging the use of closed-process methods, such as column chromatography, to improve patient safety.

Another challenge associated with technological progression in the AAV field is assessing the impact of different platform processes and purification strategies on viral attributes, such as potency and tropism. As more advanced measures of these attributes become available, it is essential to have flexibility during process development to ensure effective production and purification while staying compliant with changing regulations. Furthermore, newly developed AAV serotypes present unique challenges for production and purification, requiring adaptable and robust purification strategies to maintain final product quality and stability.

There are persistent challenges in testing for viral quality at both small and large scales, as well as controlling the quality of the development process. Common issues for quality control appear when scaling up or scaling down. Maintaining quality at either end of the scale is crucial to meeting regulatory requirements and necessitates sufficient technological capacity for consistent quality control.

INNOVATION & EXPERT KNOWLEDGE

Process development must aim to ensure cost-effective and timely C&GT production to meet rising demand and deliver critical therapies to patients. To achieve this, drug developers must apply expert knowledge to integrate innovative techniques and technologies into processes.

Process development teams should continuously search for new technologies while creating new assets for producing, purifying, and assessing the quality of C&GTs. This involves utilizing multiple techniques for evaluating product characteristics throughout the process, such as using new platforms for faster production, combinatorial chemistry to improve titers, light or mass spectrometry-based technologies for quality assessment, or novel chromatography methods for purifying high-quality products. Biopharma companies are also integrating data mining and analytics to improve their manufacturing processes. By connecting various data points, it's possible to boost yield and efficiency, decrease costs, and enhance the consistency of outputs. This type of data utilization is becoming increasingly important in the industry and will be used more in the future, although potential difficulties in integration with the existing framework could occur. Combining insights into the underlying mechanisms of disease onset with advances in biomedical engineering creates a platform for developing new C&GT delivery methods and associated cures.

STAYING CURRENT WITH CELL & GENE THERAPY ADVANCEMENTS

Manufacturing viral vectors and plasmids require specialized expertise and the integration of the latest science and technologies. With 3,649 C&GTs in the pipeline, there is a need for manufacturing support and state-of-the-art facilities and equipment.[2] In this rapidly advancing field, it is crucial to stay informed about the latest developments to meet the growing demand for C&GTs and benefit to patients.

A lack of effective treatments for certain diseases has driven many developments in C&GT technologies. In particular, many rare diseases are caused by single genetic abnormalities, but most have no existing treatments. This has pushed the need for enhanced technologies and to increase the production of gene-editing C&GTs to help this underserved patient population.

TECHNOLOGICAL ADVANCEMENTS

One of the major challenges facing C&GT developers is targeting therapeutic

delivery to the right location in the body and ensuring the immune response is minimal. These are areas in which C&GTs are constantly advancing to the benefit of the C&GT industry and patients receiving therapeutics. The development of novel serotypes and delivery vehicles like lipid nanoparticles (LNPs) allow for tissue-specific and targeted delivery of C&GT and reduce the risk of an adverse immune response. Improving the efficiency and quality of viral vectors is a significant step to achieving the desired therapeutic effect without off-target toxicities.

CRISPR-based technologies are advancements in genetic modulation that are increasingly used for C&GTs. CRISPR-Cas9 is a powerful tool for precisely cutting and editing genes, and it has been used to treat a wide range of genetic diseases, including sickle cell anemia, Tay-Sachs disease, and certain cancers. CRISPR-based gene regulation methods also hold great promise for precise and long-term expression and have the potential to change the C&GT industry through precise, efficient, and cost-effective genetic manipulation. The low costs and improved delivery of CRISPR-inserted genetic material via viral vectors enable faster timelines for scaling up and commercializing gene therapies.

FUTURE CHALLENGES IN THE CELL & GENE THERAPY SPACE

C&GT developers and manufacturers must stay informed to incorporate innovative techniques and technologies and effectively meet increasing demand. Keeping pace with the latest C&GT advancements requires attending conferences, collaborating with academia, and communicating with regulatory bodies. Proactive measures like these help mitigate potential risks and allow for timely adjustments to the industry's structure in response to new technologies and developments.

Staying abreast of advances and effective collaborations also goes beyond technology. Developing a C&GT involves multiple considerations for biopharma companies, such as regulatory compliance, establishing relationships with regulatory agencies, clinical trial design, and analytical requirements. These processes can be challenging, and partnering with external innovators can help ease the burden and facilitate successful product delivery.

MANUFACTURING TO MEET DEMANDS & QUALITY REQUIREMENTS

Aside from process development and integrating innovative technologies, progressing and reinforcing manufacturing quality is a key trend for developers within the C&GT space. This trend affects the whole biopharma industry as new companies enter the market and competition increases.

The pressure is on for C&GT companies to make the most of investment resources and bring high-quality therapeutics to market quickly to avoid costly delays in development and manufacturing. Avoiding delays requires expertise and collaboration from a manufacturing team that works closely with the analytical process development team. Additional factors like having facilities located in proximity to each other can also help streamline timelines through more effective collaboration and coordination between departments.

MEETING SCALING DEMANDS

Remaining informed about the latest developments in cell line development is crucial, particularly when it comes to cell culture. Achieving this requires expertise in both adherent and suspension production platforms. One trend in the industry is the increasing use of suspension cell cultures for scaling up C&GT production; however, adherence-based cell cultures will still play an important role in manufacturing these therapies. Being proficient in both types of cultures allows for the flexibility to accommodate the various requirements of different C&GTs products and industry demands.

Being well-informed about the needs of cell line scaling helps make informed decisions on cell line development. Instead of automatically opting for a suspension cell line for its scaling potential, an adherent cell line is more appropriate. Depending on the indication, virus requirements, or therapeutic target, an adherence-based cell culture may be more effective. External manufacturing expertise can aid in making these complex decisions, ultimately increasing the chances of success.

Creating stable cell lines will be a major technological advancement for the production of C&GTs moving forward. Instead of relying on transient transfection, the focus is shifting toward generating stable cell lines because of the following advantages:

- **Consistency of vial vector quality:** Once a stable cell line is developed, it provides a reliable cellular source of viral production with consistent quality and potency.
- **Scalability of production:** Stable cell lines can be expanded in capacity to

produce large quantities of viral vectors, which can be crucial to the commercialization of C&GTs.

- **Cost-effectiveness:** Stable cell lines can be maintained in the laboratory for prolonged periods, reducing the need for repeated isolation and expansion of cells from primary sources.
- **Time efficiency:** Stable cell lines are easy to handle and maintain, which helps with scalability and meeting short timelines.
- **Compliance:** Stable cell lines can be characterized and validated to ensure and demonstrate their consistency, purity, and identity to regulators.

KEY LESSONS

The treatment potential of C&GTs is only just starting to be realized, and the increasing demand for treatments will help drive funding in the space. As the C&GT field evolves, it is becoming more critical than ever drug developers evolved convergently. This will require developers to embrace the transformative change within C&GT and the wider biopharma industry and be open to the key trends discussed within this article.

Addressing the challenges of implementing better process development, technological advancements, and quality requirements for C&GT need a collaborative and open approach. Successfully overcoming these challenges will present opportunities for companies to thrive in the competitive C&GT industry and produce treatments of great value to patients.◆

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BIOGRAPHIES

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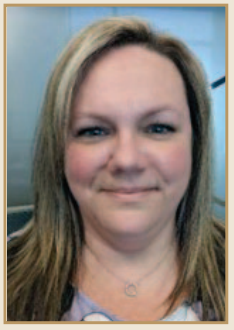

Dr. Laura A. Kerepesi is the Associate Director of Preclinical Manufacturing at Andelyn Biosciences and has been part of the Andelyn team since early 2014. She has over 20+ years of R&D experience from opportunities at Battelle Memorial Institute, Thomas Jefferson University, The Ohio State University, and Nationwide Children's Hospital. Her experience includes immunology, infectious disease, vaccine, and cancer research, viral vector process development, and preclinical upstream and downstream AAV manufacturing scale-up. She earned her PhD in Immunology/Parasitology from Thomas Jefferson University.

Cyrill Kellerhals joined Andelyn Biosciences in 2021 and oversees both viral vector and plasmid GMP manufacturing. He has over 20 years of Quality and Manufacturing leadership experience across Asia, Europe, and North America in the Pharmaceutical, Biopharmaceutical, and Medical Device industries. He earned his BSc in Chemical Engineering, and his MBA with a specialization in Business Analytics from Whitman School of Management at Syracuse University.

DEVICE DEVELOPMENT

Connected Auto-Injector Development: How to Leverage Human Factors Engineering

By: Finola Austin

INTRODUCTION

Drug delivery devices, such as auto-injectors, that allow for patient self-administration of medication, always need to ensure safety and effectiveness, whilst also, whenever possible, maximizing comfort and convenience. Connectivity adds a new dimension to these essential elements as connected drug delivery devices can capture, transfer, and display injection data, providing the user with step-by-step feedback during the injection process and reminders about future doses.

While providing a whole range of benefits, however, connected devices can also pose new challenges. Manufacturers must find a balance between offering users "enhanced" functionality whilst ensuring the added "bells and whistles" do not increase complexity and hinder ease of use. Early human factors engineering helps ensure user requirements are captured and fed into early design decisions that shape the way connectivity is managed in the medical device user interface.

Regulatory agencies also increasingly stress the importance of incorporating human factors and usability engineering throughout the design and development process. A thorough human factors process is a key constituent for regulatory submissions. In the US, for instance, the US FDA is currently reviewing the content of human factors and usability engineering standards and guidance as part of US marketing authorization.[1]

This combination of considerations is understandably making human factors analysis and user studies crucial to the advancement of connected drug delivery devices design and successful regulatory approval. The following will examine the human factors process for such devices, including a detailed look at Owen Mumford's recent development of the UniSafe® 1 mL auto-injector.

HUMAN FACTORS STUDIES AT A GLANCE

Formative and summative user testing is the best known and perhaps most feared aspect of the human factors engineering process. However, there are some key preliminary activities that must precede any user testing in order to optimize the user interface and lay the foundation for successful user testing plans and outcomes.

Preliminary activities are geared toward getting the best understanding of the intended users and their strengths and limitations, the intended context of use, and intended use scenarios. Early user research around these topics also seeks to understand the known use issues with similar devices on the market. As early concepts and ideation start to formulate, these activities help to inform the first draft of a use-related risk analysis (URRA). The URRA helps to inform and shape requirements for the user interface and continues to develop and iterate alongside the device concept. Critically, it is central to the human engineering process and helps to drive any user interface evaluation planning during the

design and development process right through to validation.

The human factors testing process involves both formative and summative studies to evaluate the intended use of a device, test the product in the intended use environments, and ensure its suitability for different user groups. Participants are recruited to resemble intended users as closely as possible, incorporating the range of most pertinent characteristics, such as age, gender, training levels, reading age, physical and sensory impairments, and previous experience.

In formative tests, the product is put into the hands of intended users early in the development process to ensure the concept is sensitive to their needs. This also helps to ensure there is sufficient time to shape the design interface and mitigate potential use errors. As the fidelity of prototype(s) grows, intended use scenarios can be simulated more closely. Formative testing should be revisited until satisfied that no further design mitigations are required. Finally, a summative test is carried out on final product equivalents of all aspects of the user interface to confirm and demonstrate the device is safe and effective for intended use.

UNISAFE 1 ML AUTO-INJECTOR

Although Owen Mumford Pharmaceutical Services has been developing auto-injectors for more than 35 years, the UniSafe 1 mL auto-injector is the first drug delivery device incorporating connectivity. With the ability to incorporate fill volumes of between 0.1 mL and 1 mL, the device aims to support patients managing a wide range of conditions, encouraging adherence to treatments and providing healthcare professionals with access to treatment data. Minimizing the risk of needlestick injuries – a requirement for all needle-based devices – was achieved by using the UniSafe sharps protection feature, with the UniSafe safety device being inserted into the autoinjector prior to use. This also ensures the device prevents needle exposure before and after the injection process. The team also simplified user steps during injection by incorporating the priming function for drug delivery into the device open/close action.

UNISAFE AUTO-INJECTOR: DEVICE DESIGN & TESTING PARAMETERS

Alongside design engineers, the human factors team looked to find a balance between providing a simple and effective user interface while still accommodating technical solutions. Emphasis on ergonomic design incorporating anthropometric data allowed developers to shape the physical interface. Psychology of user interface design contributed to key decision points around the Bluetooth connection process, placement of Bluetooth button, and power management; a key

user requirement was that the added functionality should not influence a safe and effective injection procedure.

Human factors testing on the UniSafe 1 mL auto-injector was specifically conducted to work under a worst-case use scenario. Although patients would most likely be introduced to device components by a healthcare professional, those in the study interacted with the device with no training and with no direction to read instructions before use. This allowed the team to gain an understanding of how patients were handling devices, understanding the display and controls, and interpreting the signals of connectivity before any guidance had been provided.

The human factors team looked to conduct studies on each aspect of the digital interface as soon as an acceptable level of reliability was reached. The smartphone application to go alongside the device could quickly be generated and simulated in Adobe XD before writing the software. However, device components and electronics, including the ability to connect the device, developed at a slower pace.

UNISAFE AUTO-INJECTOR: LEARNINGS FROM TESTING

Formative studies helped to evaluate the content and flow of the app and reinforced Owen Mumford's commitment to developing a "demonstrator" app to support safe and effective injection practices. As the app evolved, there was inevitable disruption to the process caused by the differing speeds of development of other device components. As a result, the team mimicked connectivity in the app during studies to get the most out of testing.

The human factors process also allowed Owen Mumford to develop generic instructions for use (IFU) in an appropriate format for users and align with potential packaging options. The best solution appeared to be a landscape booklet, allowing enough space to present intended user steps. Moreover, the team also experimented with different colors on the key touch points to guide loading and unloading of the device. This showed the impact of different colors on the user experience whilst allowing the team to assess different aesthetic and marketing proposals.

SUMMARY

Incorporating connectivity into drug delivery devices is a challenging process. Whilst there are a number of exciting possibilities, developers must create devices that remain user friendly while harnessing the latest technologies. Extensive iterative human factors studies – of both the physical and connected interfaces of a device – ensures the device design is optimized for different user groups by the time it is ready for commercial launch. ◆

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BIOGRAPHY

Finola Austin is Human Factors Lead at Owen Mumford Pharmaceutical Services. Aa a highly experienced Human Factors Engineering Manager, she boasts 15 years of experience in mentorship and management of human factors services in safety-critical industries. Her career began in Occupational Therapy within acute, long-term and community settings, and her training in accessibility has given her special insight into the needs of impaired users. Since then, she has successfully planned and delivered Human Factors activities for hundreds of hand-held medical devices, including auto-injectors, emergency use devices, inhalers, injection pens, and lancets, and is proficient in the generation and review of documentation. She has executed numerous user evaluation studies in the UK and US – including studies on safety engineered devices, injection pens, and color differentiation.

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SUPPLY CHAIN SOLUTIONS

Steady Supply in Turbulent Times: The Importance of Secure Supply Chains & Drug Packaging Integrity

By: Peter Belden

INTRODUCTION

The past 5 years have been a time of significant flux, particularly for the biopharma industry. Ensuring the security of supply chains has been increasingly challenging for biopharma in the wake of the COVID-19 pandemic and has only been exacerbated by global conflicts, rising interest rates, and fuel shortages. On top of these difficulties, supply chain integrity is a constant concern, with increasing incidences of drug counterfeiting putting the lives of vulnerable patients at risk.

Moving forward, drug developers and manufacturers must learn lessons from the past years and determine how new technologies and innovations could help provide a more resilient and robust supply chain for biopharmaceuticals. With deadlines fast approaching to ensure compliance with serialization laws in the US, these considerations must be at the top of biopharma's agenda.

The following offers unique insight into strategies that can be applied to weather the turbulent times ahead and ensure a reliable supply of critical drug products to patients. It also explores how sustainability and integrity can be attained with the right packaging and supply chain solutions.

GLOBAL EVENTS MAGNIFYING SUPPLY CHAIN FLAWS

The biopharma industry faced an unprecedented challenge at the start of 2020 in the form of the COVID-19 pandemic. Economic lockdowns in key markets, including China, India, the EU, and the US caused shortages and bottlenecks within biopharma supply chains. With many isolating and stringent rules on social distancing in place, the biopharma industry struggled to provide the necessary drug production activities to meet demand. Restrictions on travel further impeded transport throughout critical supply chains. The result was limited availability of essential drugs due to significantly longer lead times for raw materials and equipment and higher manufacturing costs.

Despite the success of the global vaccination program, the pandemic highlighted existing weaknesses in the global supply chain infrastructure, including a growing dependence on a limited number of suppliers and the vulnerability of critical raw materials. Other, more localized events, such as the UK's exit from the European Union (EU) further put a spotlight on the need to prepare for the impact of geopolitical decisions on essential medicine supply chains.

Now, in the wake of the pandemic, it is important for the biopharma industry to evaluate how the strategies used to navigate supply chain issues could be applied to overcome current challenges. These difficulties include the rising costs of raw materials, fuel, and electricity, as well as geopolitical tensions, such as the conflict in Ukraine; both of which are impacting supply chain security and sustainability.

STRIVING FOR A SUSTAINABLE FUTURE

As the world becomes increasingly aware of the impact of human activities on the environment, there has been a increasing demand for sustainable practices across all industries, including

"Despite the success of the global vaccination program, the pandemic highlighted existing weaknesses in the global supply chain infrastructure, including a growing dependence on a limited number of suppliers and the vulnerability of critical raw materials. Other, more localized events, such as the UK's exit from the European Union (EU) further put a spotlight on the need to prepare for the impact of geopolitical decisions on essential medicine supply chains."

pharmaceuticals. The pharmaceutical industry relies on complex global supply chains that span multiple countries and continents, making it challenging to ensure that every link in the chain is sustainable. However, with the right measures in place, it is possible to achieve sustainability in pharmaceutical supply chains and contribute to a better, more sustainable future for everyone.

The packaging design of pharmaceutical products plays an important role in ensuring the safety and efficacy of drug products. However, there is a growing awareness of the environmental impact of packaging. As a result, sustainability in packaging has become a critical issue for the industry. The materials used in packaging, such as plastics and metals, can have negative environmental impacts, including pollution and greenhouse gas emissions.

To address these challenges, the pharmaceutical industry is increasingly turning to sustainable packaging solutions and late-stage production methods. One example is the use of eco-friendly material alternatives, such as biodegradable plastics, recycled paper, and compostable materials. These materials can help reduce the environmental impact of packaging and can be used for a wide range of packaging formats, including bottles, pouches, and blister packs.

Another approach is to reduce the amount of packaging used in pharmaceutical products. This can be achieved by optimizing packaging design, using smaller packaging formats, reducing the size and weight of packaging materials, and minimizing the use of unnecessary components. This not only reduces the environmental impact of packaging, but can also result in cost savings for companies.

Playing close attention to procurement and stock keeping strategies to reduce destruction of components and utilizing suppliers with flexible ordering options are also important methods to reduce waste.

A STRATEGY FOR FUTURE RELIABLE SUPPLY

Considering the complexity of the challenges the biopharma industry can anticipate in the coming years, it is essential drug manufacturers learn from the lessons of the past and are proactive in implementing innovative solutions. There are many areas where biopharma developers and manufacturers could focus to build a strategy to reliably supply therapeutics to patients.

Location Matters for Supply Chains

Although the impact of the pandemic was seen across the globe, manufacturers with a strategic geographical location, such as mainland Europe, were often able to limit the impact of supply chain disruptions far better than those more isolated.

Brexit has further influenced the shift of organizations toward mainland Europe, with many companies - including biotech - having plans to relocate to countries such as the Netherlands in the years following.[1] The EMA's post-Brexit move from London to Amsterdam in 2019 has further influenced biopharma's plans to relocate, with UK-based organizations now having to spend more money and time preparing administrative paperwork for medicines to be approved in both the EU and UK.[2] In a bid to navigate the uncertainty of the biopharma regulatory framework and avoid additional costs of customs duties and tariffs, many companies have relocated to areas offering better stability.

Biopharma manufacturers should therefore carefully consider how their location and that of their supporting partners could influence supply chain stability in the future.

Prepare for a New Wave of Biologics

At the height of the pandemic, a new, revolutionary drug modality entered the spotlight: messenger RNA (mRNA) vaccines. The increasing adoption of mRNA technologies signifies our progression into a new era of novel biologic therapeutics. In 2022, new biologic modalities, such as

antibody-drug conjugates (ADCs), bispecific proteins, and cell and gene therapies (C&GTs), accounted for approximately one-third of approvals, driving biologics approvals ahead of small molecules for the first time.[3]

The sensitivity of biologics to various factors including temperature, humidity, and other environmental factors, can significantly impact their transport in supply networks. In preparation for this shift toward biologics, drug manufacturers must adapt and strengthen the relevant supply chains to ensure their robustness and ability to withstand the challenges ahead, while balancing that with the responsibility to further sustainability initiatives.

Agility With Postponement Packaging

Postponement packaging can be a valuable strategy to reduce unnecessary waste and enable greater agility in responding to changes in demand. By leveraging digital printing solutions coupled with a careful procurement strategy finalization of products for the markets can be left until closer to the point of use, allowing biopharma companies more flexibiliy and responsive to the changing market.

In addition to reducing unnecessary waste, inventory costs and lost product can also be reduced. Postponement packaging also enables the product to be packaged and labeled based on the most up-to-date information available.

JUGGLING SUSTAINABILITY WITH PACKAGING INTEGRITY

It is important to remember sustainability will not be the only issue drug developers and manufacturers will encounter in the future. As well as making supply chains more sustainable – from the sourcing of raw materials to optimizing processes – drug producers must ensure the integrity of the product's packaging.

Without secure packaging solutions, therapeutics could be at higher risk of counterfeiting, possibly placing patients' health in danger as a result. The World Health Organization (WHO) estimates that up to 1 in 10 medicines in less economically developed countries could be counterfeit.[4] This problem extends even further; in 2020, officials at the Pharmaceutical Security Institute uncovered 4,344 incidents of counterfeiting, theft, and illegal diversion of pharmaceuticals in 137 countries.[5]

HITTING PHASED SERIALIZATION ADOPTION DEADLINES

Serialization will continue to be fundamental in ensuring a safe and secure supply chain. By assigning a unique serial number or code to individual units of a drug product at packaging, the product can be tracked as it moves through the supply chain, from manufacturing to distribution and ultimately to the patient. The tracking and tracing offered by serialization can improve patient safety by preventing entry into the supply chain of counterfeit or substandard drugs.

In many countries, serialization is a legal requirement, and regulatory authorities have established guidelines and standards for implementing serialization systems. In 2013, the US Congress passed the Drug Supply Chain Security Act (DSCSA) to reinforce biopharma supply chain safety and security with an established, uniform system for tracking and tracing prescription drugs. It requires all prescription drugs to have a unique product identifier, which includes a serial number, lot number, and expiration date.

The DSCSA was implemented in a phased approach, with various requirements and deadlines for compliance. The next deadline for phased adoption is November 27, 2023, when trading partners will be required to add serialized product data to the transaction information when the product changes ownership.[6]

If not sufficiently prepared for the November deadline, the biopharma industry can expect significant delays, as distributors will be prohibited from accepting or selling products failing to meet DSCSA requirements.

ADOPTION OF BLOCKCHAIN TECHNOLOGY SOLUTIONS

As well as serialization, the use of blockchain technologies could offer additional security to biopharma supply chains. These technologies can allow for more secure, transparent, and tamper-proof digital record-keeping with a permanent and unalterable record of all transactions in the supply network. Blockchain could also help facilitate more transparent collaboration across multiple pharmaceutical supply chain partners, reduce service lead times, and promote information sharing through a secure digital chain. Ultimately, serialization and blockchain technologies could further connect the whole industry, from manufacturer to patient, potentially improving communication and minimizing potential delays as a result.

LOOKING AHEAD

The pandemic helped shine the spotlight on the weaknesses of biopharma supply chains and the potential risks posed to patients and the future of the industry. With growing numbers of biopharma companies aiming to meet the growing demand for novel biologics, including personalized and customized medicines, the biopharma industry must strengthen its supply chains to improve sustainability and security.

Learning from the previous challenges of the pandemic, those in biopharma should carefully consider their approach to building an optimized supply chain for future sustainable supply of critical medicines. By implementing techniques like postponement packaging, minimizing waste by optimizing the design of a packaged product, and considering territorial location, biopharma producers will be in a strong position to respond to future difficulties. ◆

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BIOGRAPHY

Peter Belden is President of Tjoapack's US Facility. With 25 years of service to pharmaceutical and biotech clients, including packaging, third-party logistics, and related commercialization offering's he joined Tjoapack to guide the growth strategy and deliver excellence for company's clients. In his pivotal role, he diligently oversees all business operations within the US region, contributing significantly to Tjoapack's strategic endeavors.

THERAPEUTIC FOCUS

Effect of NE3107 on the Pharmacokinetics Profile of Carbidopa/Levodopa in Patients With Parkinson's Disease

By: Joseph M. Palumbo, MD

INTRODUCTION

Parkinson's disease is a progressive, debilitating neurological disease that currently affects about 1 million people in the US, with a 20% increase in the number of impacted patients throughout the next 10 years. The one symptom most people think about in Parkinson's is tremors, especially in the hands, although patients can also experience tremors in their legs, jaw, or head.

Aside from tremors, other common symptoms of Parkinson's include muscle stiffness, balance and coordination problems, and slow movements. The disease also causes many non-movement symptoms, including dementia, emotional problems like depression, urinary issues or constipation, skin problems, and difficulties with speaking, swallowing, and chewing.[1]

Usually, symptoms begin gradually and get progressively worse over time. Multiple studies are underway to understand what impacts a patient's risk factor of developing Parkinson's, but thus far, age is the only clear factor that raises someone's risk. Most Parkinson's patients develop the disease after they reach 60 years of age, but 5% to 10% see their symptoms develop before they turn 50.

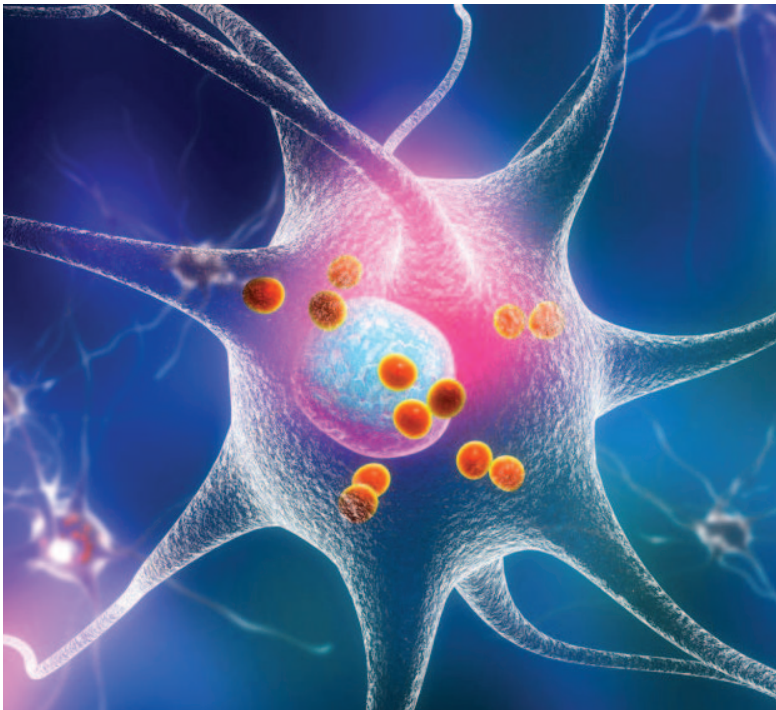
STANDARD OF CARE IN PARKINSON'S DISEASE

The primary driver of Parkinson's pathogenesis and progression is rapidly declining levels of dopamine in the patient's brain. Dopamine is the chemical that transmits messages between the nerves that control muscle movements and those related to the brain's pleasure and reward centers.

Thus, the current standard of care is a drug called levodopa, which helps replace the lost dopamine in the brain. Initially considered a wonder drug, levodopa was originally prescribed to Parkinson's patients more than 50 years ago, and the standard of care hasn't changed over this period of time.

However, long-term use of levodopa may cause problems for some patients, with the most significant side effect being levodopa-induced dyskinesia, a type of tremor that develops when the drug is used for too long or at too high a dose.[2] Additionally, although the hallmark movement disorders associated with Parkinson's tend to respond well to levodopa, it lacks disease-modifying potential and doesn't help much with other non-motor symptoms, including dementia, emotional problems like depression, urinary issues or constipation, skin problems, and difficulties with speaking, swallowing, and chewing.

Furthermore, levodopa's effects typically only last about 4



hours, which means the drug tends to wear off overnight while the patient sleeps. As a result, patients often wake up with their Parkinson's in the "off state," meaning their symptoms are not well-controlled because their medication has worn off.

This off state is typically characterized by muscle rigidity and difficulties getting out of bed in the morning. One of the hopes for Parkinson's treatments is finding a therapy that will extend patients' "on state," or the period during which their movement-related symptoms are well-controlled, meaning they retain sufficient muscle control.

Today, most Parkinson's patients are treated with a combination of levodopa and carbidopa, which decreases the peripheral conversion of levodopa into dopamine. The result is reduced gastrointestinal side effects and an increase of levodopa bioavailability in the patient's central nervous system, where it is most needed and offers the greatest benefits.[3]

THE ROLE OF NEUROINFLAMMATION IN PARKINSON'S PATHOGENESIS

Many proposed treatments aimed at improving upon levodopa's effects or adding onto them are currently in development. These proposed new treatments for Parkinson's address the disease from different angles. One of the most interesting avenues of attack in Parkinson's and many other diseases is aimed at reducing inflammation. Throughout the past 30 years, researchers have learned that Parkinson's patients experience inflammation in their brains.[4] However, it's only been in recent years that inflammation has come to be seen as one of the root causes of the disease rather than a result of it.

In fact, several studies have demonstrated that patients taking non-aspirin, non-steroidal anti-inflammatories(NSAIDs) have a significantly reduced risk of developing Parkinson's.[5] As a result, researchers are starting to believe halting the immune response could be the key to keeping Parkinson's from progressing.

Because of the chronic inflammation in Parkinson's patients, it's believed that humoral immunity, the process of adaptive immunity via the production of antibodies by B cells, might play a critical role in the disease's progression. On the other hand, T-cell immunity might have a greater impact in the onset of the disease.[6]

Digging deeper into the inflammatory drivers of Parkinson's disease revealed the importance of the inflammatory pathways comprising extracellular signal-regulated kinase (ERK) and nuclear factor-kappa B. These pathways form a feedback loop triggering oxidative stress that drives neurodegeneration. By targeting the ERK pathway, we should be able to halt this feedback loop — thereby minimizing the progression of Parkinson's or possibly even stopping it in its tracks.[7]

NE3107'S IMPACTS ON THE CARBIDOPA/ LEVODOPA COMBINATION

Given the longevity of treatment with levodopa + carbidopa and the positive effects it has brought for many Parkinson's patients, eliminating it entirely from the standard treatment regimen doesn't make sense. However, much can be done by building upon the benefits of treatment with that combination while making up for its shortcomings.

Addressing Parkinson's via the inflammatory pathway offers a unique perspective that was virtually unheard of only 10 years ago. One such treatment that targets neuroinflammation in Parkinson's is BioVie's drug candidate, NE3107, which is currently in Phase 2 clinical trials. It's showing significant promise for patients treated with it and the levodopa + carbidopa combination.

NE3107 is an oral molecule that can cross the blood-brain barrier, binding ERK and inhibiting the pro-inflammatory pathways without affecting homeostatic functions. In a marmoset model of Parkinson's, treatment with NE3107 improved mobility, enhanced the activity of levodopa, and decreased levodopa-induced dyskinesia and neuronal death in the substantia nigra.[8]

Following the marmoset study, a Phase 2, double-blind, placebo-controlled trial was initiated to evaluate the efficacy, pharmacokinetic effects, and safety and tolerability in Parkinson's patients also treated with the levodopa + carbidopa combination. The trial looked at these factors over a 27-day period.

The trial planned to enroll 40 patients between the ages of 30 and 80 and randomize them 1:1 to receive 20 mg of NE3107 twice daily or a placebo for 27 days. All participants had been diagnosed with Parkinson's disease, had responded to levodopa treatment, and experienced bradykinesia as a symptom. Patients had been taking 300 mg of levodopa/carbidopa daily and had experienced "off states" in the early morning.

The Phase 2 trial found that 6 of 20 patients treated with NE3107 and levodopa/carbidopa experienced an on state in the morning after their levodopa had been withheld overnight for at least 8 hours and before taking their morning

dose of levodopa. However, none of the 19 patients receiving the placebo reported an on state the morning after their usual Parkinson's medications had been withheld for at least 8 hours overnight.[9]

Prior to the set of data on patients who received NE3107 being in the on state the next morning, another data set assessing the efficacy of the drug was released. In general, patients who had received NE3107 and levodopa experienced at least a 3-point improvement in their score on part 3 of the Movement Disorder Society Unified Parkinson's Disease Rating Scale (UPDRS) versus those who received only levodopa.

Part 3 of this scale assesses patients' motor-related symptoms, and a 3-point improvement on this test is clinically meaningful. In fact, patients under the age of 70, presumably with less-advanced disease, experienced at least a six-point improvement in this score.

Before commencing the Phase 2 trial of NE3107, participating patients who didn't receive their Parkinson's medications for at least 8 hours overnight were assessed using the UPDRS first thing in the morning. Then they received their medication and were scored using the UPDRS again at 1, 2, 3, 4, and 8 hours after administration.

The findings that indicated 6 of 20 patients receiving NE3107 were in the on state first thing in the morning were consistent with the results from a previous non-human primate study, demonstrating the intrinsic promotoric activity of the drug candidate.[10]

Due to the positive results in the Phase 2 trial, plans to launch Phase 3 potential pivotal trials to continue the development of NE3107 for Parkinson's disease are underway.

SUMMARY

The preliminary observational data from the latest Phase 2 clinical trial indicates that NE3107 shows promise for Parkinson's patients. The finding that this treatment enables a meaningful percentage of patients to be in the on state when they awaken the morning after receiving it is particularly significant. Having trouble getting out of bed in the morning has an especially negative effect on the patient's quality of life, and it's clear more treatments offering this benefit are needed.

Dr. Anthony Lang, the Jack Clark Chair for Parkinson's Disease Research at the University of Toronto, who was not involved in the aforementioned clinical trials, described the data as "encouraging." He added "Morning off symptoms cause significant impairment of movement and disability for patients with Parkinson's disease. A potential treatment that can address this symptom is an important therapeutic need." ◆

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BIOGRAPHY

Joseph M. Palumbo, MD, LFAPA, MACPsych, is Chief Medical Officer of BioVie Inc., where he leads the research and development functions. Dr. Palumbo has held prior Chief Medical Officer and senior worldwide governance roles at BioPharma, including the most senior scientific title at Mitsubishi Tanabe Pharma in both the United States and Japan, with earlier global leadership experiences in European and American pharma. Dr. Palumbo earned his BA from the University of Pennsylvania and a Doctor of Medicine from the George Washington University School of Medicine, where he is a member of the Medical School Council of Advisors. He was a Biological Sciences Training Program Fellow of the National Institutes of Health and chief resident for the Abraham Ribicoff Clinical Neuroscience Research Unit at Yale University.

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MEDICAL DEVICE TESTING

Breathing Component Biocompatibility: The Practical Application of ISO 18562

By: Luminita Moraru, MSc

INTRODUCTION

The Medical Devices Industry has grown and is expanding daily. With this in mind, manufacturers must prove the safety and effectiveness of the products before being used in humans. All over the world, US, EU, and Asia, authorities are reviewing the data considering similar bullet points.

The world has faced the COVID19 crisis, and during these times, many medical device manufacturers have designed breathing devices to save lives. The safety of these ventilators had to be proven and the risk versus benefit measured.

Respiratory devices are classified as indirect contact medical devices as per *ISO ISO10993: Biological Evaluation of Medical Devices and are being assessed following ISO18562: Biocompatibility evaluation of breathing gas pathway in healthcare applications* standards.

Even if breathing medical devices are assessed by a different standard, the process to submission is similar to direct medical devices. The first step is assessing the risk, and for this, information gathering is mandatory for the Biological Evaluation Plan (BEP). At this stage, the next steps are defined. If the information is incomplete or the risk is not minimized, further testing is required.

For contact medical devices, extractables and leachables studies, degradation studies (when the potential for degradation exists), chemical characterization, and often animal testing, are required as per *ISO10993: Biological Evaluation of Medical Devices*.

For indirect contact medical devices, specifically breathing devices, a similar approach is required. The main difference is

TABLE 1

Exposure Category	Length of Patient Exposure	Patient	Bodyweight (kg)	TTC (ug/day)	Breathing Volume (m3/day)
Limited Exposure	≤24 Hours	Adult	70	360.00	20.00
		Paediatric	10	51.43	5.00
		Infant	3.5	18.00	2.00
		Neonate	0.5	2.57	0.21
Prolonged Exposure	>24 Hours but <30 Days	Adult	70	120.00	20.00
		Paediatric	10	17.14	5.00
		Infant	3.5	6.00	2.00
		Neonate	0.5	0.86	0.21
Permanent Contact	≥30 Days	Adult	70	40.00	20.00
		Paediatric	10	5.71	5.00
		Infant	3.5	2.00	2.00
		Neonate	0.5	0.29	0.21

the assessment of the potential extractables and leachables is performed using gas to simulate real-life scenarios. The main focus is to gather data about any materials that could be released in the gas pathway and inhaled by the user. While in direct contact medical devices in which the chemical data is generated using extraction solvents, temperature, and different time conditions, breathing medical devices are tested by simulating the worst-case scenarios, and instead of using extraction solvents, the "extractables and leachables" released into the gas pathway are analyzed, and the extraction vehicle in this study is the air.

THERE ARE 4 PARTS OF THE STANDARD

ISO18562-1: Biocompatibility Evaluation of Breathing Gas Pathways in Healthcare Applications - Evaluation & Testing Within a Risk-Management Process

This document presents the key steps that need consideration when assessing breathing devices. The most important is the information gathering process and the Biological Evaluation Plan before any testing is performed. The standard guides on the different types of patient groups, breathing volumes, body weight, and Threshold of Toxicological Concerns.

ISO18562-2: Biocompatibility Evaluation of Breathing Gas Pathways in Healthcare Applications - Tests for Emissions of Particulate Matter

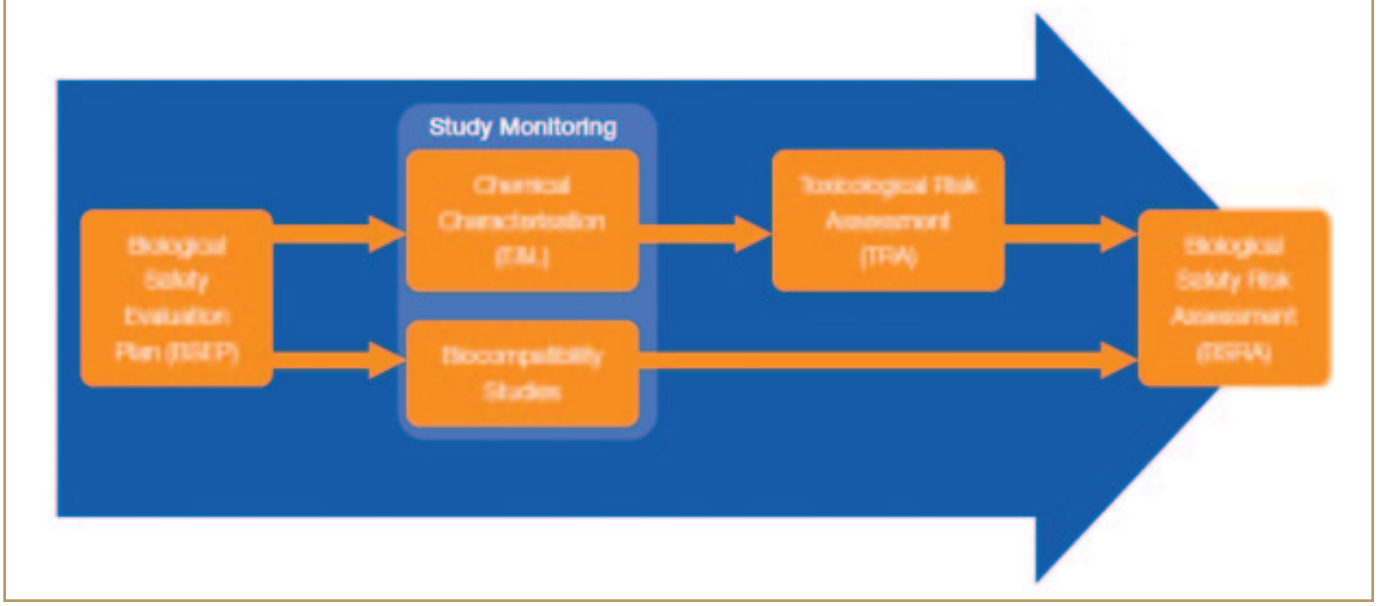
The standard is presenting different ways of simulating the worst-case scenario for any particulate matter to be released from the medical device and that can land on the patient's lungs. For this test, the highest flow rate is considered as the worst-case scenario as more particulates can be released when the device is working harder to provide more air. Only particulates with a diameter more than 0.2 μm are of interest for this study. There is a maximum allowable mass limit of 12 $\mu g/m^3$ of accumulated particulate mass, without differentiating the size.

When the size of the particulates is differentiated, the limit for the particulates with a size between 0.2 μm and 2.5 μm has a maximum limit of 12 $\mu g/m^3$, while the mass of particulates with a size between 2.5 μm and 10 μm cannot exceed 150 $\mu g/m^3$. The evaluation must consider the expected service life, any expected or processing or reprocessing, and patient contact.

ISO18562-3: Biocompatibility Evaluation of Breathing Gas Pathways in Healthcare Applications - Tests for Emissions of Volatile Organic Compounds (VOCs)

In this part of the standard, the focus is on any volatile organic compounds that can be released by the breathing device during use. As some volatile organic compounds (VOCs) can become gas at room temperature, and to simulate the worst-case scenario, testing must be performed at the highest clinically relevant temperature. This accelerates the volatilization of any potential harmful materials. The flow of the testing is also one crucial parameter to consider, and the lowest clinically relevant flow is considered as the most appropriate as it slowly allows the volatiles to be released and be absorbed.

IMAGE 1



As per ISO18562-1, different patient groups breathe different volumes of air per day and have different body weights. The permitted concentration of the volatiles is adjusted considering these details. The standard states that any materials below 2 $\mu g/m^3$ are not to be reported.

ISO18562-4: Biocompatibility Evaluation of Breathing Gas Pathways in Healthcare Applications - Tests for Leachables in Condensate

This part of the standard only applies when there is potential for condensation to form during the clinical use of the medical device. The rationale is that the condensation could lead to materials leaching from the device's pathway and contacting the patient. The standard presents the testing requirements, and testing involves a polar (water) extraction performed at body temperature (37°C) of the gas pathway components. If possible, the device should be run as in real-life and the condensate to be collected and tested. When this is not possible, an extraction of the relevant parts is performed. The extract is followed by a screening for semi-volatile organic compounds and metals. As part of the study, cytotoxicity and sensitization must be assessed as there are not known in-vitro adequate methods.

Same as ISO10993, ISO18562 classifies medical devices based on their duration of use in direct or indirect contact with the user:

- Short-term exposure or limited exposure: Medical devices whose sum of single, multiple, or repeated duration of use does not exceed 24 hours.
- Prolonged exposure: Products whose cumulative sum of single, multiple, or repeated contact time is likely to exceed 24 hours but not likely to exceed 30 days.
- Long-term exposure devices or permanent contact: Cumulative sum of single, multiple, or repeated contact time exceeds 30 days.

Knowing the duration of use of the medical device is very important as this dictates the testing periods, mainly for VOCs in which ISO18562-3 splits the duration of the testing based on the duration of use.

SUMMARY

At the end of the testing period, all the data is captured and must be assessed in the Toxicological Risk Assessment in which all materials are evaluated for any toxic effects. If toxicity data is not available, TTCs presented in ISO18562-1 are used.

When the end points of the Toxicological Risk assessments are addressed and the device is deemed as having an acceptable toxicological risk from clinical use, the Biological Evaluation Report can be put in place, reviewing that all the recommendations made in the Biological Evaluation Plan have been addressed and the device is safe to be used.

The Biological Evaluation Report is the last step in the process and all the data is reviewed and concluded if the results are satisfactory. In conclusion, even if breathing medical devices are not captured by ISO10993 standards, the approach of proving the safety is identical. ◆

BIOGRAPHY

Luminita Moraru is the Analytical Chemistry Manager at Medical Engineering Technologies Ltd. with 7 years of experience in Medical Device Testing. She is an individual expert committee member of *ISO10993: CH/194 Biological Evaluation of Medical Devices and ISO18562: CH/121/09 Lung Ventilators & Related Equipment* having insight knowledge 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 Master's in Chemistry at the University of Bucharest and is a Member of Royal Society of Chemistry.

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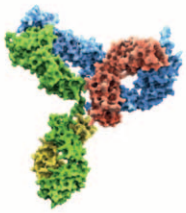

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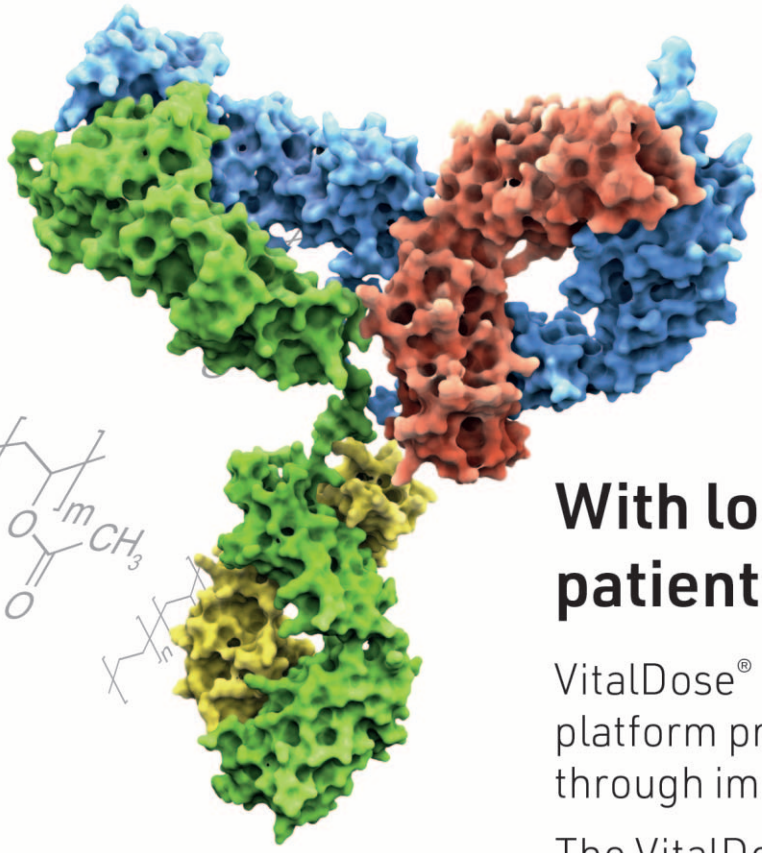

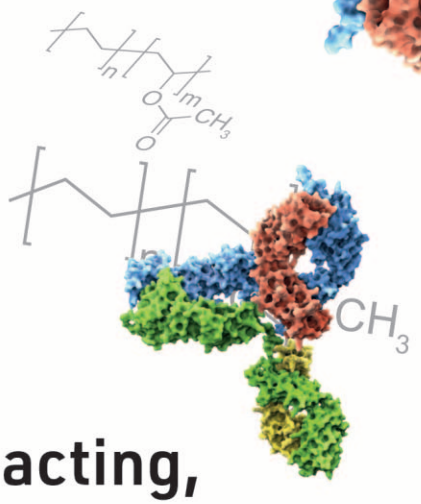

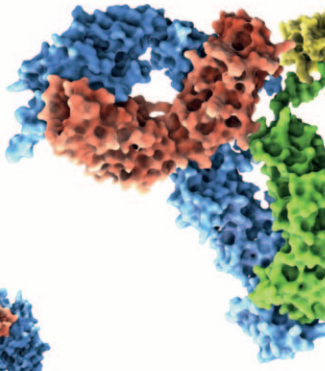

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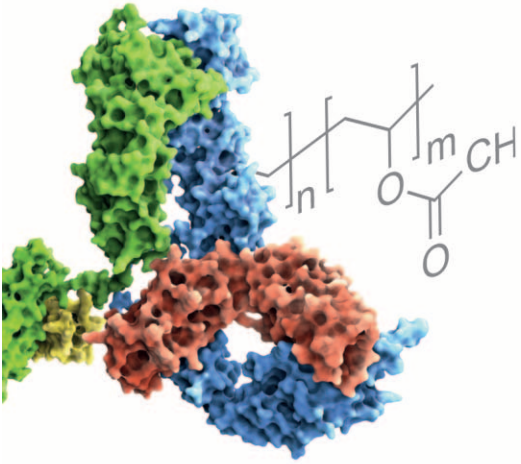

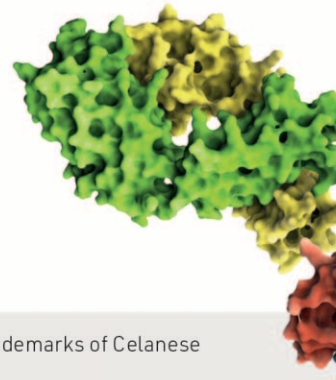

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Sever Pharma Solutions

Sever Pharma Solutions: Development & Manufacturing of High Potent Polymer-Based Dosage Forms

Sever Pharma Solutions (SPS), formerly Q-Pharma, is a CDMO headquartered in Malmö, Sweden, offering expertise in polymer-based, high potent drug product dosage forms, such as intravaginal rings (IVRs), and has been in business since 1975. In 2021, the former Q-Pharma rebranded itself as SPS and acquired Foster Delivery Science Inc. (FDS) in Putnam, CT, later that same year. FDS got in the business doing hot melt extrusion (HME) to enhance bioavailability of poorly soluble molecules and subsequently leveraged this technology to produce various drug delivery dosage forms, such as implants, IVRs, and films. SPS employs more than 350 staff members, and more than 35 are in its Putnam, CT, site. The Malmö site is focused on commercial manufacturing and development of novel dosage forms and IVRs, and solid oral dose products are also commercially manufactured at this site. The Putnam site focuses on the development of polymer-based dosage forms and manufacturing of early to late-phase clinical materials and commercial manufacturing. The company's expertise in Malmö and Putnam is based on polymer processing technologies, with a focus on extrusion in Putnam and both extrusion and injection molding in Malmö. SPS's Putnam site has downstream capabilities, such as milling, tablet compression, or capsule filling for oral dosage forms, and tight tolerance extrusion and cutting for implantable dosage forms. The implant capabilities include micro-diameter implants for ocular and intra-tumoral use. SPS offers end-to-end solutions to clients, committed to their client's success through the whole journey, including offering regulatory support.

Drug Development & Delivery recently interviewed Tony Listro, Vice President of Technology and Site Lead for SPS's North American site in Putnam, CT, to discuss the company's recent focus areas as well as current plans for expansion.

Q: Why do you emphasize your ability to handle HPAPIs in polymer-based dosage forms?

A: The potency of HPAPIs creates a challenge from a handling standpoint as these molecules are ranked in the highest occupational exposure bands (OEB) up to and including OEB6. SPS has policies, procedures, and capabilities in place, allowing us to handle high-potent drugs in small and large quantities to meet our client's needs in the challenging high-potent drug development and manufacturing field. While they may create a handling challenge, HPAPIs are very beneficial because their potency allows for a reduced payload in the final dosage form for the API to be effective. HPAPIs are important because their potency helps deliver treatment in a highly targeted manner with limited side effects. In addition to limiting side effects, combining HPAPIs with polymer-based implantable dosage forms helps to create dosages that enable patient compliance with steady plasma levels without systemic side effects.

Q: You mention the SPS Putnam Site (previously FDS) got its start offering hot melt extrusion (HME) services to enhance bioavailability of poorly soluble molecules. What are SPS' HME capabilities and processes?

A: SPS is a CDMO providing services from proof of concept through clinical and commercial manufacturing services in polymer-based drug delivery systems, literally milligrams to kilograms. HME is a technique employed to enhance the performance of drug molecules exhibiting poor water solubility or poor bioavailability. Laboratory techniques are used to screen the thermal stability and solubility performance of the API in polymer systems. Oral dosage forms, such as tablets and capsules, are developed and manufactured using HME technology. Formulations are tailored to meet clients' desired profile for drug release using pharmaceutical-grade polymers and other excipients. SPS uses state-of-the-art twin screw extrusion technology. Processes are custom designed and developed to enhance drug release. Scale up is performed from lab (milligrams to grams) to commercial-scale volumes (grams to kilograms). Tablets are formulated to deliver stable, effective dosage forms with optimal drug release. Products are characterized using in depth analytics.

Q: How does the acquisition of FDS fit SPS's growth strategy in the US?

A: SPS has been present in Europe for decades, the company needed to expand, and FDS was Sever's first US acquisition, marking the company's presence in North America. The Putnam site is a 32,000-sq-ft facility and has tripled in size post-acquisition. We invested $3.2 million during 2022, and the facility currently operates three GMP manufacturing suites and is continuing to expand. The site has added packaging capabilities, an extrusion suite, a blister suite, and an oral dosage form suite with tableting, tablet coating, and automated capsule filling capabilities. 2023 has driven a $6-million investment adding two fully functional HPAPI suites, one for development and one for GMP. SPS plans to add a 40,000-sq-ft commercial manufacturing facility within the next 2 years, with the ability to increase to 60,000 sq ft.

Our demand is driven by small molecules being poorly soluble, and HME is an environmentally friendly and economical strategy, keeping the manufacturing process continuous and very suitable for robust industrial-scale manufacturing of drug delivery systems. SPS wanted to expand its polymer processing technology platform to include HME as well as manufacturing implants into micro-implants for ocular and intra-tumoral use. At the Putnam site, we develop and manufacture dosage forms with these polymer processing technologies.

Q: What is Sever's approach to sustainability and innovation?

A: Interestingly, we have seen an uptick in interest in HME because it is a solvent-free process. There has always been an interest in HME for continuous manufacturing, especially because the process has a small footprint and defined unit operations in the process. Our HME technology is an important offering to help our clients meet their sustainability goals. Our knowledge of the process technology allays our clients' fears. HME is a highly controllable process, and we have the process design technology and understanding to help our clients meet their desired endpoints.

Internally, we have a corporate objective to be carbon neutral by 2040. An increased focus on sustainability is just part of being a good corporate citizen. Being a Swedish company, SPS is concerned about the environment and energy consumption. Automation is becoming a priority for us as we

plan to leverage this technology to enable faster growth. Many products we manufacture require manual assembly. Automation technology to manufacture products faster and more accurately than manual processes is out there, and we are experiencing a big push to automate our manufacturing processes.

Q: How do you see the polymers market and the CDMO segment shaping up in 2023?

A: We are seeing growth in the polymers area. Polymers mainly used for contraceptive or hormone replacements are growing, such as local drug delivery in the ocular space or in oncology, particularly in the past 18 months. The widespread adoption of polymers for controlled drug release in several indications is driving solid growth in the coming years. We can extrude very tight-tolerance products, which is key in this space. An important topic of interest will be in high-potent drug development, and we are making big investments there. SPS is continually interested in expanding its capabilities to work with new polymer technologies and growing its expertise beyond conventional bio-durable and biodegradable polymers for long-acting implants and controlled release. New polymer technologies require new processing technologies, and that creates a challenge we always enjoy overcoming.

Q: What is going to be the main priority for SPS in 2024?

A: In 2024, we will have our new HPAPI suites fully functional with identical twin screw and single screw extrusion technologies in both our development and GMP suites. We plan to enable our growth with new project management software technology to help our clients gain more visibility to their programs as they progress from development to manufacturing. To continue our leadership position in the markets we serve, we plan on hiring new staff, and continuing to strive to be an extension of our clients' companies. We only succeed when our clients succeed. We have a technology roadmap that includes organic growth through continued investments in process technologies. ◆

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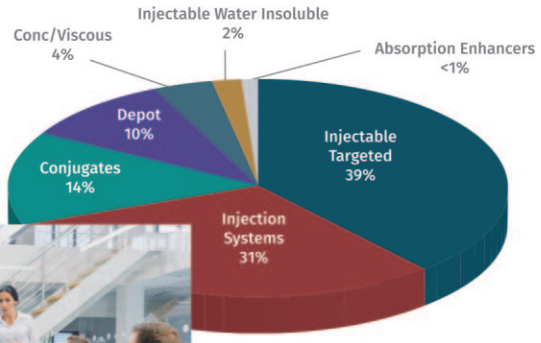

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Special Feature

Injection Devices: Designing for Sustainability, Usability, & Digitization for Patient Compliance

By: Cindy H. Dubin, Contributor

The global injectable drug delivery market could reach $1.317 billion by 2030, fueled by the prevalence of life-threatening diseases, the development of smart wearable devices, and the Internet of Things (IoT), which makes it possible to collect valuable data directly from injection devices.[1] Prefilled syringes, autoinjectors, and pen injectors are all expected to become more popular as pharma companies seek alternatives to oral dosage regimens and deliver long-acting drugs in an effort to improve patient compliance.

Drug and device developers do face a bit of an uphill battle as they tackle challenges related to delivering viscous and large-volume biologics, preserving the integrity of sensitive formulations, regulatory issues, and manufacturing scalability. "Intravenous therapies are often cost-intensive and require certain patient compliance to achieve cost-benefit targets," says Markus Hörburger, Product & Service Manager at Vetter. "To simplify adherence and patient convenience, many companies with products that fit this profile are reformulating their therapies for subcutaneous delivery. While that step has upsides for patients and drug owners, it can present some significant technical challenges for current injection device formats."

Cecile Gross, Global Category Manager, Parenteral at Nemera agrees: "A user-friendly device for a seamless delivery fosters patient acceptance. But high-viscous biologics increase administration challenges as it is related to a patient's pain perception. We need to make sure that subcutaneous administration is not painful to increase compliance and adherence."

Viscous and/or large-dose products require devices configured to manage much higher delivery-related forces, extended injection times, or both. Meeting those specific requirements can mean extensive device customization, additional development and QA processes, and numerous other cost- and time-intensive investments. Mr. Hörburger says: "Drug owners need to consider these factors as early as possible in their therapy's path to a combination product format."

Experts say another consideration is smart or connected devices that play a key part in patient adherence. The challenge is embedding the technology to be as user friendly as possible. "Digital health adoption requires the addition of connectivity without adding complexity to the devices, all in an effort to manage disease and treatment," says Ms. Gross.

And there also exists a balancing act between usability and sustainability. Developers face the challenge of growing concerns over the disposability as many devices are intended for single-use and need to be discarded after use.[2] Efforts are being made to ensure reusability and recyclability into the device design. "While sustainability is a growing priority across the biopharma industry, disposable injection devices present a direct challenge to this greater goal," says Mr. Hörburger.

Catalent Biologics provides fill/finish & device assembly for sterile products.

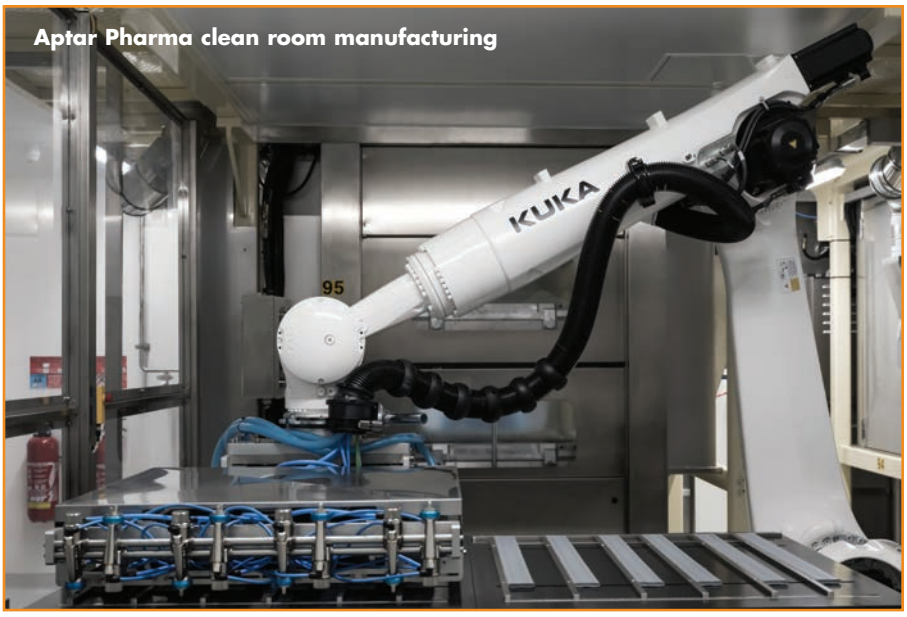
This exclusive annual report from *Drug Development & Delivery* highlights how leading device and drug companies are working to address the challenges of usability, sustainability, and technology to increase patient compliance.

Aptar Pharma: Quality, Safety & Regulatory Compliance for Elastomeric Closures

In the pharmaceutical industry, the safety and efficacy of injectable drugs are paramount. One of the leading causes of recalls by the FDA for injectable drugs is particulate contamination, which can lead to adverse reactions. As the industry evolves and regulatory standards become more stringent, manufacturers are under increasing pressure to ensure the particulate cleanliness and safety of their products. Furthermore, with the prevalence of biologics and biosimilars in development pipelines, it is primordial for drug manufacturers to reduce their development risks and select a partner that will accelerate their access to the market, says Estelle Verger, Business Development Senior Manager, Aptar Pharma.

The recent revision of Annex 1 by the European Medicines Agency's Good Manufacturing Practices (EMA GMP) has further underscored the importance of contamination control. This revision mandates that manufacturers not only have a robust contamination control strategy in place for their operations, but also extends this requirement to their upstream supply chain.

As a leading manufacturer of closure components, Aptar Pharma developed PremiumFill® – a state-of-the-art solution in the realm of elastomeric closure components for injectable drugs, she says.



Aptar Pharma clean room manufacturing

"Manufactured in ISO-classified cleanrooms and utilizing state-of-robotization, PremiumFill vial stoppers and syringe plungers offer improved specifications on particulate, fiber contamination, and overall product quality," she says. "This ensures that patients receive injectable drugs that are both safe and effective by minimizing the risk of contamination. This also supports pharma customers in demonstrating the implementation of a comprehensive Contamination Control Strategy in compliance with Annex 1 revision. Additionally, PremiumFill can significantly reduce scrap rate on fill-finish lines, leading to cost savings and increased production efficiency."

A recent case study, conducted by a leading injectables manufacturer, showcased the tangible operational benefits of PremiumFill. Upon integrating PremiumFill into their filling operations, the manufacturer reported a decrease in scrap rate by more than 20%, without requiring any process adaptation, explains Ms. Verger. "A deeper dive into the data revealed that the primary contributors to this reduction were related to fiber contamination and staining of the elastomer – both of which are comprised in PremiumFill's enhanced specification," she says.

To further improve their operation and fully leverage the advantages of PremiumFill, drug manufacturers can choose Aptar Pharma's Ready-to-Use (RTU) gamma-sterilized components. In addition to guaranteeing sterility at the point of use, thus meeting Annex 1 revision guideline for sterility assurance, Aptar Pharma RTU products are packaged in bags without Tyvek, which is a known source of fiber/particle contamination, Ms. Verger explains. Furthermore, PremiumFill product can be packaged in Rapid Transfer Portbags (RTP) that connect directly onto filling lines' isolators to limit the risk of particulate contamination and facilitate compliance to Annex 1 revision regarding contamination control.

She says: "As the pharmaceutical industry grapples with the dual challenges of ensuring patient safety and complying with evolving regulatory standards, Aptar Pharma's range of solutions help customers achieve operational efficiency and meet ever-increasing regulatory standards."

Supporting Combination Product Development

BD regularly conducts a combination of primary market research, human factors, and clinical research studies to understand the patient experience, and applies these insights to injection device design and combination product development. BD is focused on high growth areas such as obesity and diabetes, as well as other leading chronic diseases. "We aim to apply BD's organizational insights on patient experience, together with our injection expertise, to support treatment of chronic disease and transition to new care settings while positively impacting patients," says Beth McBride DiLauri, Director, Portfolio Marketing, BD Medical-Pharmaceutical Systems.

BD recognizes patient experience can impact adherence and treatment outcomes. With its BD Libertas™ Wearable Injector (still in development) program as an example, the goal is to enable transition of care to new settings by shifting from intravenous (IV) to subcutaneous (SC) delivery. To de-risk that transition, BD conducted patient and pharma interviews as well as multiple generative and formative human factors studies in an iterative cycle to inform usability and patient experience with a wearable combination product. BD also conducted its own clinical study of the BD Libertas Wearable Injector. This study assessed key parameters, including subject tolerability and device acceptability that can impact patient experience. Amongst the findings was the confirmation that 100% of subjects were likely to use the BD Libertas Wearable Injector, if prescribed.[3] "We see this as a leading indicator of positive patient experience and compliance," she says.

In addition to the patient experience, BD recognizes that there are multiple key decision criteria that inform pharma's choice when selecting the optimal device for a given combination product. BD Medical-Pharmaceutical Systems provides a broad portfolio of parenteral drug delivery systems, including glass and plastic prefillable syringes, safety and shielding systems, and advanced drug delivery systems, including pens, autoinjectors, wearable and on-body injectors. The company also offers a range of combination product development testing services.

Assembly options available for BD Libertas™ Wearable Injector

One pharmaceutical company approached BD for support after facing significant challenges in the market related to needle-shield removal and syringe flange breakage, seemingly driven by the interface between their chosen primary container and secondary devices, explains Ms. McBride DiLauri. "Leveraging our extensive expertise and a solution consisting of a fully integrated prefilled syringe and disposable autoinjector, coupled with robust supportive data, BD helped the customer address the issues they were facing, leading to a successful filing and regulatory approval for their new combination product."

BD Libertas Wearable Injector is a product in development; some statements are forward-looking and subject to a variety of risks and uncertainties. BD Libertas Wearable Injector is a device component intended for drug-device combination products and not subject to FDA 510(k) clearance or separate EU CE marked certification.

Catalent Biologics: Helping Clients Through Device Selection

Catalent is focused on the assembly and packaging of delivery devices to meet its customers' requirements, thereby supporting the needs of its patients. The company partners with its customers to provide the equipment that is necessary for assembling prefilled syringes into devices. It also provides assembly services both for customized devices as well as for the majority of pre-designed autoinjectors and safety devices.

"When pharma companies come to Catalent for assembly services, they usually rely on its expertise to help guide them through the device-selection process for their therapies," explains Brian Galliher, Principal Engineer, Catalent Biologics. "Catalent's experience is based on many years of assembling multiple types of devices for different therapies, and ensuring

that the assembly equipment are compatible with patient needs."

One particular customer posed a unique challenge for Catalent with a therapy that required a treatment volume of 2mL. The original size of the syringe administering this dosage was 1mL, requiring the patient to administer two injections for each treatment, describes Mr. Galliher. "The Catalent team worked diligently with this customer to qualify a 2mL autoinjector, which allowed the patient to reduce the number of injections, increase their safety, and improve the ease of use and overall patient compliance."

Credence MedSystems, Inc.: Solving Problems with Needle Clogging & Steel Incompatibility

As injectable therapies become more complex, greater challenges arise in delivering these injectables to provide patients and healthcare providers a user-friendly experience. "A syringe with a pre-attached needle ("staked needle") is the gold standard in our industry, vastly preferred compared to the alternative of requiring the user to attach the needle at the time of use," says Laxman M. Halleppanavar, Head of Portfolio Strategy and Management, Credence MedSystems, Inc. "There are significant usability benefits resulting from the use of a pre-attached needle, including reduced likelihood of user error in attaching the needle, fewer user steps and shorter preparation time, and compatibility with autoinjectors for device-assisted injections."

However, there are circumstances that have traditionally prevented use of a pre-attached needle. Drug formulations that either include suspensions and viscous solutions with the propensity to clog a needle or demonstrate incompatibility with steel or tungsten have prevented use of a pre-attached needle because the needle is in contact with the drug during storage. Without the use of a staked-needle syringe, compatibility with autoinjectors becomes limited. The end-user's experience is therefore negatively affected, which is especially problematic with the ongoing trend wherein delivery of medications moves from formal healthcare settings to administration at home.

Credence MedSystems focuses on identifying problems and bringing innovative design and development to solve these problems and enhance the end-user experience. "The Credence Isolation Valve™ technology solution enables all the end-user benefits of a pre-attached needle to be realized even with drug formulations that pose needle-clogging risk," he says. The Credence Isolation Valve prevents the drug from migrating into the needle lumen during storage, therefore eliminating the needle-clogging risk. When the user or autoinjector applies appropriate pressure, the valve opens, allowing the drug to travel through the needle into the injection site. The Credence Isolation Valve is pre-mounted into a standard staked-needle syringe prior to filling and the syringe arrives to the filling suite pre-sterilized and ready for filling. Because of the valve's low profile, typical fill volumes can be achieved for any specific syringe barrel size.

For drugs where compatibility with steel or tungsten is the problem, Credence offers the Stainless Steel-Free Companion syringe. The Credence (SSF) Companion Syringe™ is a derivative of Credence's Dual Chamber Syringe™ platform, utilizing a front stopper to completely isolate the drug product from any exposure to the needle during storage. "Therefore, despite the formulation challenges, the user still benefits from a pre-attached needle as well as all of the demonstrated usability enhancements that come along with Credence's Companion® needle-retraction technology," says Mr. Halleppanavar. At the end of the injection, the user feels and hears an end-of-dose cue in the form of a click, and then the needle retracts into the syringe, preventing accidental needlestick and syringe reuse.

The Credence Isolation Valve Prefilled Syringe enables all the end-user benefits of a pre-attached needle to be realized even with drug formulations that pose needle-clogging risk.

He concludes: "With the end-user in mind and an openness to implementing

new approaches, Credence is enabling the gold standard of a pre-attached needle to be employed even with challenging drug formulations. This, combined with autoinjector-assisted injections and Credence's needle-retraction technology, provides user enhancements to healthcare professionals and self-injecting patients."

DDL, Inc.: Reliable & Sensitive CCI Testing

The global injection device market is driven by increasing prevalence of chronic diseases, technological advancements in self-administration, higher occurrences of needlestick injuries coupled with a rise of biologic drug products. All these factors are leading to a rise in the overall use of combination product devices such as prefilled syringes and autoinjectors for drug delivery. Industry has observed a dramatic shift away from the use of glass vials and single-use syringes to prefilled syringes, pens or autoinjectors. The ease of drug administration with these devices has increased patient compliance, which ultimately has been the 'end-goal' for these devices.

Not only are the devices evolving, so are the drug products themselves, points out Aaron Liss, Director of Sales & Marketing, DDL, Inc. For instance, pharmaceutical companies are deploying drug mechanisms such as nanoparticles and microspheres in drug suspensions to enhance targeted delivery and control the release of APIs post injection.

DDL is focused on the safety testing of the devices and performing various services for combination product companies. These unique devices (prefilled syringes, autoinjectors, pen injectors) have very specific FDA requirements that are outlined in various guidance documents and standards. One of the rapidly growing and evolving safety tests for injectable devices is Container Closure Integrity (CCI) testing utilizing deterministic methods governed by USP <1207>. CCI refers to the ability of a primary container closure system to maintain product integrity and prevent contamination or leakage.

Historically, combination product companies performed sterility and/or probabilistic ingress methods to evaluate this critical endpoint for regulatory submission. "Unfortunately, sterility and ingress methods have presented inherent issues for the life science industry," says Mr. Liss. "For instance, sterility and microbial ingress rely on microorganisms and the absence of microbial growth as the 'indicator' for a passing result."

However, false positives and false negatives can easily occur when performing sterility and microbial ingress methods. False positives can result in huge, negative financial impacts for companies if they are not able to invalidate the result and instead are left with no other option than to scrap the lot of product. False negatives hold higher risks because this outcome can result in adverse patient safety events and product recalls. Dye ingress has the challenge of subjectivity when performing it qualitatively by visual inspection. Dye ingress methods are better suited for gross leak detection during a full package validation under ISO 11607, he says.

For these reasons, industry experts began creating and drafting deterministic methods for CCI testing. The four primary CCI deterministic tests include helium mass spectrometry, high-voltage leak detection, vacuum decay, and laser headspace analysis.

These methods do not use biological systems such as microorganisms. Conversely, deterministic CCI methods use highly sensitive analytical equipment to detect leaks down to 1µm, depending on the method. "Deterministic CCI methods do not present the same inherent issues as sterility and ingress methods," says Mr. Liss. "In addition, the limit of detection for deterministic CCI methods are much more sensitive and reliable once your method is validated."

Duoject Medical Systems: Safer Self-Administration of Reconstituted Injectables

Duoject has a long-standing expertise in the design and development of injection devices, drug reconstitution systems, safety features, and ergonomics. As a result, the company has been concentrating its efforts on two avenues in recent months. The first area of focus is to create systems that will make it simpler to reconstitute drugs, while the second involves combining drug reconstitution and injection into the same device. Both of these can make it easier to prepare and administer drugs safely at home, explains William G. Fortina, Business Development Director, Duoject Medical Systems. "Additionally, even though these devices are likely to cost more than conventional vial or syringe formats, they will reduce the overall cost of healthcare because they would remove the need for hospital visits or medical assistance. Patients can access more complex products from the convenience of their own homes while saving time thanks to the development of such integrated and user-friendly devices."

Custom drug delivery systems for clients are a specialty of Duoject Medical Systems. For novel, difficult therapies, custom systems are typically required. The company's engineering team prides itself on working with difficult drug requirements

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(like large volumes, high viscosity, temperature sensitivity, etc.) while making sure the systems are user-friendly, error-proof, and safe. "To keep the cost of filling and sterilization processes competitive, we frequently advise clients to use common primary containers like vials, cartridges, and syringes," says Mr. Fortina. "To achieve the desired outcome, we then create administration or reconstitution systems around these standard containers."

Reusable systems for injectable medications present challenges, the main one being sterility requirements. Guaranteeing sterility for a single-use injection device is one thing; guaranteeing sterility for multiple use is much more challenging. Reusable injection systems face additional difficulties due to the possibility of needlestick injuries and cross-contamination. To avoid safety and regulatory challenges, he says most of Duoject's clients choose to steer clear of reusable injection systems.

One notable exception is the use of injection pens, which are commonly used for insulin treatments. Building on this widespread adoption, Duoject has developed a single-use drug reconstitution device called PENPREP EVO. This single-use drug reconstitution device enables users to perform drug reconstitution from a vial and fill a standard 3mL cartridge with the admixture, then subsequently use it with a pen injector of their choice. This allows patients to use their injection device multiple times for ongoing medical care.

In recent months, several clients have approached Duoject to find solutions that combine drug reconstitution and injection in a single device. "There are many advantages to combining these two processes into a secure, user-friendly standalone device," says Mr. Fortina. "Healthcare professionals would save time on drug reconstitution and administration in hospital settings. Risks from needlestick injuries and dosing mistakes would also decrease. Patients may be able to self-medicate at home thanks to such systems. Benefits in this scenario include time savings (no trip to the clinic is necessary), the ability to complete the task at home without the assistance of a healthcare professional (user-friendly device operation), and possibly improved treatment adherence."

Enable Injections: Mechanical On-Body Delivery System

Enable Injections' mission is to improve the patient experience. From the beginning, by designing with the patient in mind, the enFuse drug delivery system has been developed to allow medications to be delivered with a hidden needle, greater flexibility for the patient and provider, and permit mobility during administration. A study published in the past year reports: "This wearable drug delivery device simplifies drug administration and could help address some of the challenges associated with self-injection, such as complicated infusion preparation, needle phobia, and concerns about pain."[4]

The enFuse is the first purely mechanical on-body delivery system, which operates silently without a motor or battery. enFuse utilizes elastomeric technology to deliver a low-pressure injection, which may confer potential clinical benefits. In addition, enFuse utilizes the original container closure for the drug rather than a prefilled cartridge. At the time of use, the user inserts the original vial into the Vial Transfer system and the contents transfer completely without further user input.

Patient-centric features include a small, hidden needle, which has the potential to positively impact patient compliance, says Jennifer Estep, Senior Director, Global Marketing & Commercial Strategy. enFuse allows for mobility and flexibility during administration. As the study stated: "Wearable drug-delivery systems have emerged as useful tools for optimal management of chronic diseases because they provide advantages over conventional subcutaneous drug delivery, including real-time drug regulation, and improvements in patient adherence and quality of life."

Additionally, patients in the study stated unanimous preference for enFuse,

The enFuse drug delivery system from Enable Injections allows medications to be delivered with a hidden needle and greater flexibility for administration.

due to ease-of-use, increased mobility during infusion, reduced setup time, and reduced pain at the injection site. And, 95% of surveyed patients indicated a preference to switch to enFuse in the future.[4]

One prohibitive factor for patients is the size of a large-volume wearable delivery device. For patients to use an on-body injector, the device must be easy to use and easy to learn, and be comfortable and easy to handle, especially for those who have dexterity and mobility challenges. The size of a device grows quickly when pumps, batteries, and traditional vials or cartridges have to be incorporated. The larger the device, the heavier it becomes, and the more difficult it can be to ensure it remains adhered to a patient's skin at the intended location for the duration of the injection, explains Jenn Beeson, Communications Lead at Enable Injections. "A lighter, less bulky delivery device, such as enFuse with its elastomeric technology, allows the patient to have a more comfortable experience," she says. "In addition, a more discreet delivery device permits the user to go about their normal activities as they wear the injector."

The enFuse delivery system can administer 5-25mL with a single device, giving pharma companies the option to administer higher volumes subcutaneously. However, due to the complexity of biologic drug formulations, sometimes a higher volume of drug is needed. Ms. Estep says the range of volume offered by enFuse reduces formulation constraints and adds flexibility to dose-finding studies. "Using a large-volume, on-body delivery system, such as the enFuse, may allow a direct conversion from an IV to a SC formulation, eliminating the task of increasing concentrating and enabling faster entry into the clinic," she says.

Flex: The Importance of the Human Experience

Flex looks to partner with customers to improve the user experience and patient outcomes. To do that effectively, it is critical to include a significant focus on HMI – the way that users interact with and experience devices. "The importance of HMI in injection device development cannot be overstated," says Jennifer Samproni, Chief Technology Officer, Health Solutions, Flex. "As the world becomes more digital and connected, and as the point of care for more patients shifts increasingly toward the home, injection device manufacturers are responsible for ensuring that their products are innovative, efficient, and user-friendly. By focusing on the needs and experience of the full spectrum of end users, and making HMI a priority in injection device design, we can improve patient care, enhance user experience, and ultimately save lives."

Flex develops injection pens, wearable injectors and pumps, and autoinjectors. One is the Smart Syringe 2.0 platform, which automates data collection for clinical trials, is made from recycled resins and recyclable, and is compatible with existing syringe packages. The other is a voice-controlled autoinjector demonstrator designed to enhance the dose-delivery user experience. The new device pairs with a smartphone app, which guides the user with step-by-step instructions.

"The autoinjector's HMI design, which provides prompts when needed and allows voice activation to "start" and "stop" the injection directly, addresses users' issues with pressing buttons on autoinjector devices," she explains. "By focusing on elegant, user-friendly HMI solutions, we can provide more intuitive and user-friendly experiences for patients who require ongoing management of chronic conditions."

While improving outcomes and patient experience are important elements for companies to consider, they are not the only ones. Healthcare companies are under increasing pressure to achieve sustainability goals, says Ms. Samproni. The smart autoinjector design platform was designed to enable MedTech and pharmaceutical companies to accelerate time-to-market, reduce costs, and boost reliability while ensuring patient compliance and sustainability needs. The smart autoinjector platform uses numerous eco-smart designs, such as:

- Long-life rechargeable batteries instead of disposable non-rechargeable batteries;

The Flex Smart Syringe 2.0 platform automates data collection for clinical trials, and is made from recycled resins.

- Secure remote upgrades for firmware on the autoinjector platform;
- Smaller subsystems and PCBA systems that use fewer materials lowers the overall CO_2 emissions; and
- Easy disassembly, better-enabling repair, refurbishment, or parts separation for reusing, recycling, or disposal.

The design adheres to DfE guidelines and principles by minimizing welding and gluing of internal products during the assembly and manufacturing process, which results in benefits even at the end-of-life stage. Because of the lower contamination of materials being recycled, the design continues contributing to lower waste targets, she says.

Along with eco-smart design considerations, a cradle-to-gate lifecycle assessment is performed to evaluate environmental impacts based on:

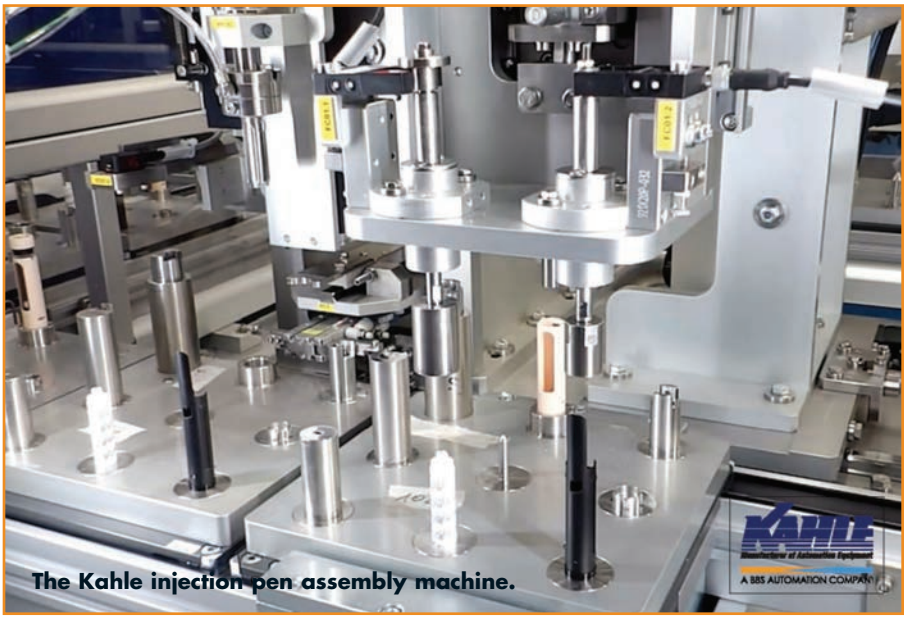
- CO_2 emissions
- Energy and water consumption
- Recycling rate (percentage of material recycled)
- Recovery rate (percentage of material used to generate energy when the product reaches the end of life)

"By prescribing to DfE guidelines with the autoinjector platform, Flex is enabling an eco-smart circular production model that ultimately reduces waste and generates higher values from resources," says Ms. Samproni. "These processes are vital as more industries, especially healthcare, continue to move towards sustainable devices that contribute to environmentally focused goals without compromising device reliability and patient safety."

Kahle Automation: Custom Automation for Drug Delivery Devices

Reusable injection devices designed to accept prefilled syringes or drug cartridges are improving adherence and treatment outcomes through innovative designs. As these therapy-specific designs are developed, many utilize microcomponents with unique features requiring complex assembly. According to John Wuschner, Vice President Engineering at Kahle Automation, getting these designs from small batch to high-volume production quantities benefits from automation for three main reasons:

- **Efficient Speed:** High volume by definition would make this reason obvious, but the assembly of injection devices requires more than just going faster, it requires a higher level of complexity. Feeding of the components without causing damage is critical here when one considers that disposable needle assemblies are produced at speeds of over 1,300ppm. Ensuring the sharp stays sharp and the functionality of the device is maintained all the way to the customer is challenging at these speeds. "Even the reusable pen injectors themselves with their intricate settable dosage dials have to be carefully threaded together at speeds of 400ppm," says Mr. Wuschner.
- **Consistency:** Automated processes are designed to mitigate the risks of assembly by having six-sigma process capability proven in advance of application to the line. By so doing, not only is the probability of rejects reduced, but also the key performance indicators of the product can be managed to generate results that perform equivalently lot to lot. Performance consistency in the device translates to shorter learning curves and leads to greater adherence by the patient, he says.
- **Quality:** While process control is paramount, automated systems also benefit from an array of quality controls that can also be integrated at these high speeds. Needle tip geometry can be inspected through computer vision inspection of the tip, functional tests can be performed to ensure patency of the fluid path or proper actuation forces, and even cosmetic indicators can be used to verify that components were



The Kahle injection pen assembly machine.

manufactured to critical specifications or that the proper components are being assembled in cases where one line produces several variants of a product family.

If identified, a rejected component (or partial assembly) can be segregated from further operations (reducing wasted components) and placed in a controlled container to avoid mixing rejects with valid product. Data can be automatically collected to identify where the defect occurred and cataloged by position, process, etc. to allow trending and data analysis to be performed. This aids root-cause analysis and helps prioritize the continuous improvement process for the line. Coupled with a SCADA system, this data can be automatically delivered to factory support personnel via production monitors and even triggered as alerts on smartphones based on thresholds customized by the user. Products can also be labeled or marked/tagged with lot control features during production or even serialized. In the event of a major non-conformance at later stages, these features allow for easier segregation of suspect product from valid product.

"These three motives for automation together form a foundation for efficient production of devices which, in concert with the device design, help enhance the patient experience through consistency and high reliability while also reducing the overall unit cost," says Mr. Wuschner.

Nemera: Patient-Centric Device Design

Patients are at the heart of development and integrated in product design as early as possible at Nemera. Cecile Gross, Global Category Manager, Parenteral, at Nemera, says this engagement allows a better understanding of patient pain points and enables the company to adapt devices to meet their unmet needs.

One of Nemera's key focuses is its on-body injector platform, Symbioze™, to administer complex, large-volume drugs such as mAbs with an adjustable flowrate to fit patient and drug administration profiles. The reusable injection device couples a reusable electronic part with a disposable one; the latter contains the prefilled drug cartridge. "This systems reduces the number of steps for the user and risk of misuse," says Ms. Gross.

Nemera also offers Safe'n'Sound®, which is intended for novice users as well as patients with dexterity issues. In order to help them manage the removal of the needle cap, Nemera has developed an overcap, an intuitive Rigid Needle Shield remover. Nemera can also offer a "look and feel" customization option, including color coding and bimaterials for a 'soft touch.'

Finally, PenOne is a disposable, fixed-dose, spring-assisted pen injector platform, which has been marketed across different countries for a variety of applications, including osteoporosis. Ms. Gross says: "As this platform has been developed with patients in mind, it is equipped with an automatic and ergonomic side release button, which allows patients to stabilize their hand during self-administration, enabling the injection of the complete dose. There is no extendable push button at the top of the pen, leading to an adequate total length of the pen. And the fixed dose means there is no risk of under- and overdosing." A dose-counter shows how many doses are left in the pen.

She adds that all of Nemera's devices and capabilities are offered to its pharma partners in a holistic way, starting from front-end development. That includes, but not limited to: the patient journey; technology screening and evaluation; device development and pre-clinical supply; and connected device UI/UX design.

Owen Mumford Pharmaceutical Services: Accounting for Volume & Viscosity

Sustainability is a key area that has grown significantly in importance for many pharmaceutical companies in the past few years. Owen Mumford shares this focus as well as the drive to net zero via Science Based Targets. They are B Corp-certified and have recently developed a new UK manufacturing site built to BREEAM standards.

"In line with these activities, we are also developing a reusable autoinjector that is a companion device for our 1mL UniSafe® safety syringe," explains Michael Earl, Director of Pharmaceutical Services, Owen Mumford Pharmaceutical Services. Weighing only 5g, the safety syringe is the only disposable element. With a two-year shelf life, the autoinjector has a mechanical design and ensures that the drug can always be delivered to the patient. The device features an LED indicator that shows both dose progression and completion, as well as audible prompts to guide the patient and provide reassurance of successful drug delivery. A lifetime battery supports the user interface so no charging or docking is required, helping to reduce complexity for the user.

The UniSafe autoinjector has built-in connectivity for data exchange between the patient and the healthcare provider, allowing patients to schedule and track their injection regimen to improve medication adherence. Data transfer is via automatic Bluetooth® communication that is initiated

The Aidaptus 2-step single-use autoinjector platform from Owen Mumford Pharmaceutical Services.

when the shroud is pressed onto the injection site, so there are no additional user steps. The device can be used with a smartphone app to provide the patient with information and alerts related to their treatment, Mr. Earl says.

He goes on to explain that changes in formulation are an inherent part of injectable drug development from the early stages through clinical trials and into post-commercialization and lifecycle management. These changes in both volume and viscosity can impact the selection and design of devices for subcutaneous drug delivery.

"At Owen Mumford Pharmaceutical Services, we have created Aidaptus® a single-use autoinjector that provides flexibility for formulation changes in a single device," he says. Aidaptus can be used with both 1mL and 2.25mL prefilled syringes in the same compact base device with minimal change parts. There is also a choice of springs to allow delivery of a range of viscosities. In addition, using novel auto-adjust plunger technology, the device automatically adapts to different fill volumes during final assembly. Using the same device for variations in formulation helps to streamline documentation, simplifies regulatory filing, and may reduce the requirement for human factors testing. The benefits from an operations perspective are a reduction in SKUs and complexity in supply chain, and in terms of capacity upscale, the same equipment can be used for final assembly. Owen Mumford is collaborating with Stevanato Group for Aidaptus using their combined experience and capabilities to manage the commercial scale up of the device.

Phillips-Medisize: Opportunities for Reusable Devices

Making significant improvements to the 2-step disposable mechanical devices that dominate the autoinjector market is challenging. But there are growing opportunities for reusable devices, especially electromechanical versions that combine the benefits of size, simplicity, and ease of use associated with disposable mechanical devices, with superior visual and audible feedback throughout the injection process and at end of dose.

In addition to reusable autoinjectors employing prefilled syringes with staked needles being used to deliver liquid stable drugs, electromechanical devices can improve patient experience in the preparation and delivery of lyophilized drugs from dual-chamber cartridges. "The need for patients to reconstitute these drugs before use is a significant disadvantage for medication self-administration," says Tony Bedford, Commercial Director at Phillips-Medisize. "But lyophilized formulation is increasing as it can reduce or eliminate the need for cold chain storage and trans-

Phillips-Medisize's Aria smart autoinjector is a powerful, flexible, platform, designed for ease of use with a compact form and aligned to key emerging global trends.

portation of biological drugs, which otherwise adds considerably to their carbon footprint."

He says the recent approval of the Skytrofa autoinjector is a good example of how an electromechanical autoinjector can improve patient experience, and we see growing interest in this format. This autoinjector, designed and built by Phillips-Medisize with a partner company, was developed to deliver Skytrofa (lonapegsomatropin-tcgd), a human growth hormone administered weekly and indicated for the treatment of pediatric growth failure due to inadequate secretion of endogenous growth hormone. Compared to the daily injections required for most other growth hormones, patients on Skytrofa required 86% fewer injection days per year. "The benefits it offers around guidance and support during preparation and administration of the drug have been recognized by several design and innovation awards," says Mr. Bedford.

Patient compliance relies on minimal user burden and clear feedback to reduce user errors. Phillips-Medisize's Aria reusable autoinjector provides a familiar configuration for established single-use autoinjector users and a non-intimidating experience for naïve patients, explains Iain Simpson, Commercial Director, Phillips-Medisize. He says: "Drugs requiring frequent injection can increase associated wastage, especially when using a more user-centric device than a prefilled syringe. Reusable devices reduce wastage considerably. During development we performed a full lifecycle analysis that showed reductions of over 50% of the amount of device-related waste compared to disposable autoinjectors."

Mr. Bedford adds: "Data from existing electronic autoinjectors shows adherence can be improved through their use, leading to better medication outcomes. Furthermore, wireless connectivity and companion digital services can enable better patient support via an app or remote healthcare professional support using real-time use data. Development of digitally-mediated behavioral change techniques is showing promise in addressing medication nonadherence and we expect this trend to continue."

Replicating the user experience of a predicate device also supports compliance with generic or biosimilar drugs. Phillips-Medsize's Envoi disposable pen injector provides biotech companies with a cost-effective entry into the generic insulin and GLP1 markets, improved by shorter travel of the activation button, making the device easier to use for large doses or by patients with smaller hands.

Both gentleman see a move towards less frequent administration enabled by the formulation of complex high-concentration biologics with larger viscosities and volumes than previously delivered, but without the need for larger volume delivery systems such as patch pumps. "Electromechanical devices can generate the larger forces required to deliver these drugs, without concern for spring-based devices stalling or inconsistent delivery times impacting patient satisfaction and compliance," says Mr. Bedford.

Phillips-Medisize is collaborating with a pharma customer to deliver a highly viscous drug that could only be delivered using a mechanical autoinjector or prefilled syringe with a much larger needle. Another customer is looking at partial dosing from a prefilled syringe to increase dosing flexibility, enabling dose titration and a reduced number of SKUs required to support weight-based dosing. Partial dosing might also offer benefits in clinical development where flexible dosing can support dose ranging studies, says Dr. Simpson.

Portal Instruments: PFS Addresses Variety of Injection Challenges

Critical factors in patient comfort and compliance are injection duration and pain. As the market evolves and high-volume and viscous formulations become more prevalent, Portal Instrument's PRIME device is designed to adapt to those changes while still prioritizing the patient's well-being, explains Dr. Patrick Anquetil,

PHD, MBA, CEO of Portal Instruments. This is encouraged by findings from early clinical saline studies, which demonstrated the PRIME device is notably less painful for self-injection when compared to a 27-gauge prefilled syringe and needle.[5]

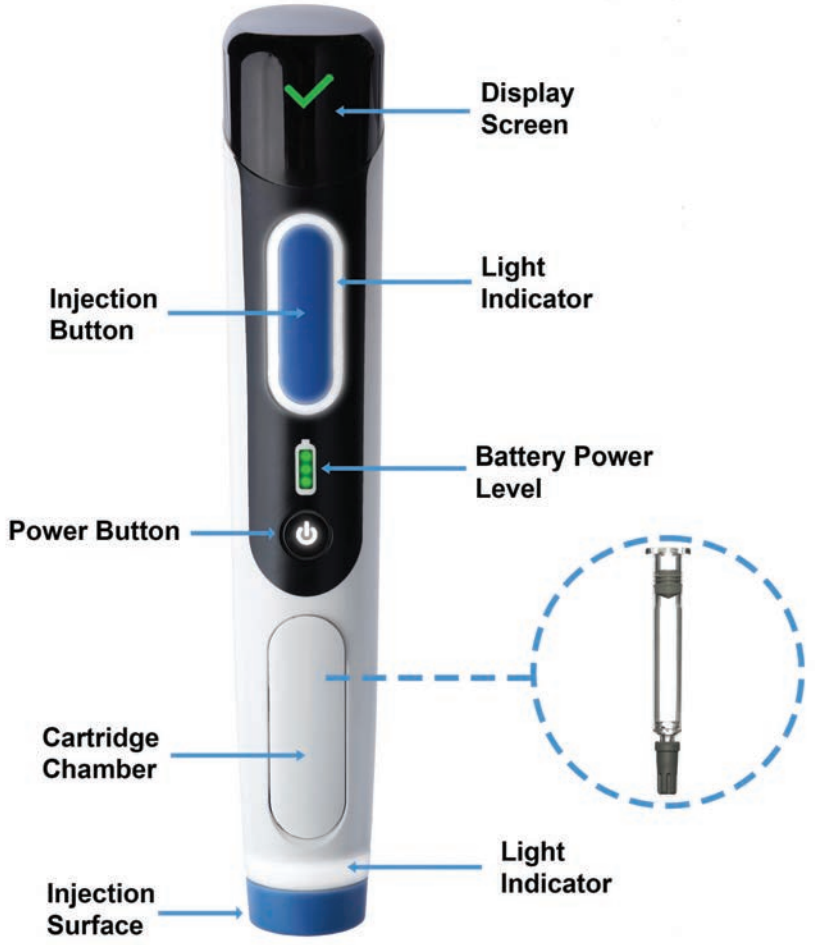
PRIME is a needle-free injection device targeting subcutaneous delivery of 1mL via a hair-sized jet in approximately 0.3 seconds. The device can accommodate a range of viscosities and concentrations while maintaining the same injection duration (~0.3 seconds). He says PRIME addresses injection challenges that arise with needle fear, injection pain, and high viscosity therapies that are often found in patients with long-term injection regimens, including, but not limited to, the areas of rheumatology, gastroenterology, endocrinology, and dermatology.

"Portal Instruments has revolutionized the idea of patient compliance through our needle-free technology," says Dr. Anquetil. "A patient-centric design coupled with cloud connectivity for real-time tracking and reminders, the device aims to foster adherence to treatment by facilitating communication with healthcare providers. The device's compatibility with standard pharmaceutical processes and data collection features can empower patients and their care team with insights, driving informed decisions and optimizing treatment outcomes."

While Portal's primary innovation revolves around needle-free administration of biologics, patient-centered design inherently aligns with environmental sustainability. PRIME is designed to be recycled after its four-year use life, and the needle-free cartridge can be disposed of in the household trash, eliminating biohazardous sharps waste.

"Incorporating the concept of reusability into the device's design can provide stability and comfort to the patient as they manage their long-term injection regimens, potentially positively impacting medication adherence," says Dr. Anquetil. "As new iterations of the device are developed, we focus on ease-of-use incorporating patient and healthcare provider feedback. Through rigorous human factor studies and interviews with disease-specific patient groups and healthcare providers, the device's design considers various patient challenges (e.g., loss of dexterity)." He adds that recent clinical study results further support Portal's efforts, with the majority (70%) of subjects selecting PRIME to be much easier or somewhat easier to use than a prefilled syringe and needle.[5]

Portal Instrument's drug delivery system PRIME is a needle-free alternative to autoinjectors and prefilled syringes for high viscosity therapies.



For many pharmaceutical companies, developing autoinjectors capable of delivering a highly viscous drug poses a significant challenge. PRIME's computer-driven technology is designed to allow viscous medications (up to 120cP) to be injected within approximately 0.3 seconds, including repeat injections with a full battery charge. Most notably, the device has been designed to administer medication from the prefilled cartridge either shortly after being taken out of the refrigerator when the drug is most viscous, or even after a longer interval (e.g., 30 minutes), with no change in the injection time. Dr. Anquetil says: "This addresses the consequences that can arise because of prolonged injection durations (e.g., early device removal) and is a game changer for pharmaceutical companies aiming to

reformulate their therapies. When a typical autoinjector's mechanisms fail to accommodate the drug formulation without increasing injection times and larger spring forces, we have provided the needle-free reusable alternative."

SHL Medical: Enhancing Patient's Independence with Connected Therapeutics

For the past 30-plus years, autoinjectors have enabled patients to take their injectable treatments outside of the healthcare setting. With the pandemic further facilitating a detachment between patients and healthcare practitioners, demands for connected technologies that support at-home care continue to rise. Managing the expectations of patients, healthcare practitioners, policymakers, and payers has therefore become a central issue when developing new digital technologies for home-based treatments.

As with introducing any new technology to the market, there are multiple, sometimes divergent, but always complex, macroenvironmental influences that need to be managed. For self-injection devices in particular, the power of digital health through connecting and digitalizing new or existing treatment modalities is yet to be uncovered, despite the numerous efforts put forth by device and pharmaceutical companies alike.

"The gap between conceptual testing and generating real-world value often impedes innovation," says Nils Weber, Global Head of Emerging Technologies and Digital Health at SHL Medical. "Therefore, new connected autoinjector solutions should safeguard the same ease of use for patients while also ensuring manufacturability, circumventing potential regulatory roadblocks, as well as offering real value to improving treatment adherence and outcomes."

SHL Medical's Molly® Connected Cap is a compact, retrofittable autoinjector add-on that records and transmits data about patients' use of the device.

To this end, SHL Medical has developed a collaborative Innovation Partnership framework, allowing SHL and its pharmaceutical and biotechnology partners to co-develop solutions through an agile approach. This allows SHL and drug companies to refine product design through an incremental innovation model, ensuring that new solutions cause minimum disruption to the patient as well as the bio/pharmaceutical company marketing the combination product. Driven by its experience with commercializing over three dozen autoinjectors worldwide, including 17 combination product projects from the Molly® modular platform technology, SHL developed the Molly Connected Cap, a compact, retrofittable autoinjector cap add-on that records and transmits data about patients' use of the product. Upon removal from the Molly device, the Connected Cap becomes active, allowing timestamped data to be relayed through a smart data transmission hub and to the cloud, which provides audio and visual cues to patients on the timing of forthcoming injections. The connection is made via Bluetooth® Low Energy beacon to facilitate seamless data transfer, which means that pairing is not required, and that the patient's usual injection process is unchanged. An accompanying demonstration software, accessed via either a mobile app or web browser, has also been developed to further provide patients with an assistive interface to their Molly autoinjector, delivering injection reminders, injection history, and scheduled injection information. The Connected Cap was also designed with easily detachable batteries and electronics to support recycling and take-back programs.

Combined with a smart data transmission hub, an app, and cloud technology, the Molly Connected Cap is part of a therapeutics platform that can provide patients with a standalone solution for managing their self-injections, reducing the need for frequent clinic visits, and empowering patients to take control of their treatment, says Mr. Weber. The platform also enables healthcare practitioners to monitor patient adherence remotely and intervene when necessary. With the data collected, care providers and contract research organizations also have the opportunity to review patients' injection histories,

identify any deviations or missed doses, and provide timely support or adjustments to treatment plans.

"The Connected Cap platform has the potential to improve the personalization and efficiency of healthcare delivery, reduce the burden on healthcare practitioners, and enable a higher level of self-efficacy and engagement among patients," explains Mr. Weber. "With several dozen ready-to-use autoinjectors already commercialized for patient use, the addition of a supplemental connected add-on can help pharma and biotech companies reap the benefits of digital health without significant change to their autoinjector products."

Stevanato Group: Three Devices, One Goal – Patient Compliance

Stevanato Group is constantly investing in a portfolio of injection devices to meet the needs of patients and pharma companies. Each patient therapy requires a unique solution, and that's why the company has three very different products in its portfolio – the Alina® pen injector, the Aidaptus® autoinjector, and the Vertiva™ on-body delivery system platform.

"Each of the devices serves a different purpose," says Adam Stops, Head of Product Management for Drug Delivery Systems, Stevanato Group. "They are each tailored to a specific patient need, population demographic, reimbursement model, and so on – all the different aspects of the healthcare industry."

Stevanato Group also provides contract manufacturing organization (CMO) services to pharma companies to support injection device projects. "Our unique approach as a one-stop-shop provider means we can cover the entire product lifecycle, from concept definition to industrial delivery and final packaging – for faster time to market and reduced total cost of ownership," he adds.

Alina is a user-friendly disposable pen injector platform for diabetes and obesity care. It is designed for daily or weekly variable and multi-dose treatments and includes an easy-to-dial dosing mechanism, for patient comfort. Visual, audible, and tactile feedback helps ensure correct dose setting and injection.

Aidaptus is a two-step, single-use autoinjector for treating rheumatoid arthritis and cancer. Its versatile design can accommodate both 1mL and 2.25mL prefilled glass syringes in the same base device – so injections can be daily, weekly, monthly, or quarterly. And it can handle a variety of drug viscosities, making it suitable for a range of treatments, including monoclonal antibodies (mAb) and small-molecule drugs.

The Vertiva on-body delivery system platform combines a single-use pod with a prefilled and preloaded cartridge and a multi-use smart controller. It can deliver basal doses with micro-precision or full-content bolus injections, making it suitable for a variety of therapies to treat conditions ranging from cardiovascular and metabolic disorders to cancer and autoimmune diseases.

"mAb treatment is increasingly moving from intravenous injections in hospitals to subcutaneous treatment in the home," says Mr Stops. "But many of these injections are still fairly large volume – above 3mL – so Vertiva is designed to serve that patient population. The fact that the cartridge is prefilled with the drug and preloaded in the pod also reduces the number of use steps for patients."

Additionally, Vertiva is designed to strike a balance between reusability and sustainability – and simplicity for patients. The pod with the needle and drug is single-use – but the smart controller containing the electronics can be used multiple times. "The pod just snaps onto the controller using magnetic coupling," says Mr. Stops. "Simplicity for the patient helps with compliance – and even someone with arthritis in their hands can easily put the Vertiva device together. Our aim with all these devices is to keep things simple for patients to use – as that really helps to encourage compliance."

Vetter: Doing Its Part to Develop Sustainable Devices

There is a growing focus on end-user convenience and devices that support it. Formats like autoinjectors and injector pens offer a range of advantages for patients, from convenient multi-dosing for GLP1 products to easy handling for arthritic patients with compromised manual dexterity. So it's no surprise that self-injected therapies like these are increasingly in demand. But while CDMOs are eager to meet that demand, they've also focused on a closely related challenge: mitigating the environmental impact of these popular devices.

"Eventually, reusable or semi-usable formats will likely become the sustainable gold-standard solution, and these technologies are already being considered and developed," says Markus Hörburger, Product & Service Manager at Vetter. "But while disposable devices are still the industry standard, there's much Vetter can and should do to make today's autoinjector- and pen-based therapies more sustainable overall."

Rather than focus solely on the

Packaging design consultation at Vetter.

devices themselves, Vetter has zeroed in on secondary packaging as an initial opportunity to mitigate the environmental impact of current combination products. Its current capabilities already include a range of alternative packaging materials and sustainable all-paper carton configurations. "Like other CDMOs, Vetter ultimately hopes to see our industry deliver truly viable solutions for sustainable injection technology," says Mr. Hörburger. "But in the meantime, our focus is on immediately impactful strategies that help us responsibly steward natural resources – while still meeting global demand for a new generation of combination products."

Wirthwein Medical: PFS Can Be Customized for Specific Applications

Wirthwein Medical's concept and strategy for injection devices focus on supply security, reliability, and ease-of-use for customers, particularly during global crises and disrupted supply chains, which take into account the principle of sustainability, as emissions for unnecessary transport or additional packaging material should be avoided, explains Dr. Thomas Jakob, Managing Director at Wirthwein Medical.

The company's WIM Ject® ready-to-fill system consists of a syringe with Luer-Lock connection to guarantee a secure connection to standard injection needle and adapter systems. The syringe is specially coated to optimize the gliding and barrier properties and closed with a tip cap. The product is packed in a tub/nest system and then sterilized. All components are based on the ISO 11040 standard and are compatible with almost all existing filling systems in the pharmaceutical industry.

In addition to the syringe system, plungers and piston rods are also offered in various colors. Should customers require individually adapted accessories in terms of design or color, Wirthwein Medical can fulfill their requests and complete the customer portfolio as required. The company is also developing for special applications such as low-temperature applications for mRNA therapies.

"We are investing in the newest technologies, always with a focus on the highest quality," says Christoph Merhold, Head of Program Management at Wirthwein Medical. "All our developments are focused on improving patient health."

West Pharmaceutical Services Inc.: User-Centric Model for Larger Dose Injections

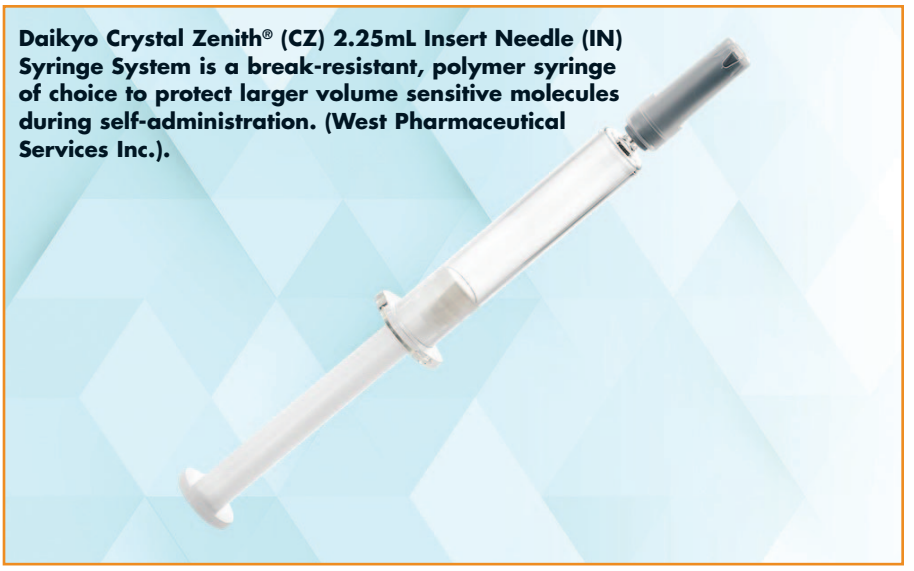
In tandem with the growing market share of biologic formulations, where higher volumes may be required to deliver the desired effect, the door has been opened to the self-administration of a wider range of biologic therapies via subcutaneous injection for applications that would previously have required multiple injections or intravenous delivery within a clinical setting. Earlier this year, West announced the expansion of its Crystal Zenith® (CZ) component portfolio to now include a 2.25mL insert needle (IN) prefillable syringe system. CZ is a cyclic olefin polymer (COP) that presents a sterile containment solution for protection of sensitive

WIM Ject® can be used for a broad range of applications e.g. Botox, hyaluronic acids, emergency drugs, infusions, as well as different pharmaceutical drugs as a prefilled syringe.

molecules and mitigates the risk of breakage, more commonly associated with glass. The elastomeric Flurotec™ plunger used in the CZ PFS system is coated with a barrier film, which reduces the risk of leachables from the elastomer and prevents absorption of the drug formulation. The film also avoids the need for additional silicone oil to be used for syringe functionality, thereby dramatically reducing exposure to a key source of protein aggregation.

The 2.25mL volume offering is an extension to the CZ 1mL IN syringe system that is currently used in the primary packaging for multiple approved drug products. "As more biologic drugs are formulated to support subcutaneous self-administration, they are often at larger volumes (>1mL) and at higher viscosities," says Victoria Morgan, Director, Segment Marketing, Biologics at West Pharmaceutical Services Inc. "As market traction on larger dose injections grows, the new CZ 2.25mL IN Syringe System will help pharmaceutical companies bring their product to patients in the most user-centric model possible."

Modern biologics, such as proteins and monoclonal antibodies, exert demanding requirements on their containment system, which can be difficult to navigate if a platform approach to packaging has been used in the past. A pharmaceutical partner of West picked their platform glass syringe system to package their new biologic drug in development, yet subsequent time pulls of stability samples showed the drug was silicone sensitive which, in turn, made the drug unstable. Analytical testing showed the presence of both visible silicone and protein in the drug product forcing the formulation team to reassess the primary packaging system.



Daikyo Crystal Zenith® (CZ) 2.25mL Insert Needle (IN) Syringe System is a break-resistant, polymer syringe of choice to protect larger volume sensitive molecules during self-administration. (West Pharmaceutical Services Inc.).

The biologic molecule required a prefilled syringe system with as low silicone oil as possible to maintain drug stability, which included both the syringe barrel and drug facing surface of the plunger. In addition, the new containment system was expected to perform as well as a glass system with respect to functionality, which includes break loose, extrusion and gliding forces, injection force, rigid needle shield (RNS) removal force, and container closure integrity. These were critical performance factors as the prefilled syringe system would be used within an autoinjector for the final drug delivery system.

"By using the CZ 2.25mL IN syringe system, West's partner was able to provide a safe and reliable containment solution to protect the customer's modern biologic, all the way to administration," she says. "The drug was stable in the CZ syringe system, and our customer was able to show better results for sub-visible particles with CZ than with glass and other polymers." The CZ syringe met USP < 1207 > for Container Closure Integrity. Functionality expectations of the syringe system were met, despite the absence of intentionally added silicone oil or other lubricants and no syringe breakage was exhibited. The partner shares: "West & Daikyo have addressed key market needs with the development of silicone oil-free (no silicone was added for functionality) tungsten-free CZ polymer pre-fillable syringe system offering, incorporating a Flurotec plunger. CZ, a cyclic olefin polymer, is a clear, biocompatible material that overcame drug-specific problems associated with glass."

Ypsomed: Catering to Larger Volumes & Fewer Injections

The self-injection market is not only growing rapidly with many new mAb-based therapies, but it is becoming more complex as injections are dosed less frequently using larger injectable volumes. Ypsomed has recently performed handling studies summarizing whether and how patient characteristics and treatment attributes influence the decision to use prefilled handheld autoinjectors or large-volume patch injectors.[6] "Performing such studies is essential to understanding patient preferences and to guide further development of Ypsomed's large-volume injection platforms," says Ian Thompson, Vice President, Account & Business Development at Ypsomed.

The company has built up a broad portfolio of autoinjectors and patch injec-

Ypsomed's autoinjector and patch injector portfolio for larger volume injections.

tors based on the YpsoMate and YpsoDose devices. All of these devices are prefilled and preassembled to ensure convenience and ease of use for the patient. Over 15 versions of the YpsoMate 1mL and YpsoMate 2.25mL autoinjectors have been launched by pharma customers for treating autoimmune diseases (i.e., RA, MS, asthma, and psoriasis) as well as for treating migraine, osteoporosis and, most recently, for cardiovascular disease. "They are all contributing to improving patient compliance for a range of patients," says Mr. Thompson.

Ypsomed developed the YpsoMate 2.25 Pro with constant spring force for more viscous injectables. He says: "Although the majority of ongoing autoinjector projects are for lower viscosities, Ypsomed has a number of ongoing customization and industrialization projects for the YpsoMate 2.25 Pro and is expanding the automated manufacturing infrastructure for future launches."

Additionally, Ypsomed supplies reusable insulin pens. While Mr. Thompson says reusable injection devices are not as convenient, as safe, or as easy-to-use as prefilled systems, they do allow the opportunity of lowering therapy costs (e.g. for insulin) and the possibility to incorporate electronics and connectivity to be integrated into therapy management systems. In fact, he says there is room for improvement to develop devices for all injectables. "The market for injection devices is growing significantly and typically the same devices are used for originators as well as biosimilars. The main innovations are focused on originator drugs being developed for larger volume, less frequently injected originator drugs."

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Drug Development
EXECUTIVE

Sesha Neervannan, PhD

Chief Operating Officer

Tarsus Pharmaceuticals, Inc.

Tarsus Pharmaceuticals: A Journey to Building a New Disease Category in Eyecare & Helping Transform Treatment for Patients with Serious Diseases

Tarsus Pharmaceuticals, Inc. is a Southern California-based biopharmaceutical company focused on the development and commercialization of therapeutic candidates to address large diseases with limited or no treatment options, starting with eye care. Tarsus is advancing its pipeline to address diseases with high unmet need across therapeutic categories including eye care, dermatology, and infectious disease prevention.

XDEMVY™ (lotilaner ophthalmic solution) 0.25% was approved by the FDA in July of 2023 for the treatment of *Demodex* blepharitis, a prevalent eyelid disease. XDEMVY has the potential to help millions of patients in need.

Drug Development & Delivery recently interviewed Sesha Neervannan, PhD, Chief Operating Officer of Tarsus, an industry veteran with more than 25 years of drug development experience, to discuss the company's innovative approach to creating a new treatment category for eyelid disease and the company's strategy to advancing other treatments in their pipeline.

Q: Tell us about Tarsus and its approach to drug development.

A: When Tarsus was founded, the leadership team identified a significant unmet need in eyelid health with *Demodex* blepharitis, a common yet often overlooked eyelid disease that impacts approximately 25 million eye care patients in the United States. *Demodex* blepharitis is caused by an overgrowth of the *Demodex* mite – a microscopic parasite that is found on nearly all humans. Despite its high prevalence, before the approval of XDEMVY, there were no FDA-approved therapies to treat the disease. Existing management options like lid hygiene have been largely ineffective for most patients. Millions of patients have this disease, yet few in the industry were giving this common, often debilitating disease much attention. We saw a unique opportunity to tackle this disease and do it differently – by targeting the underlying biology and root cause of the disease. Instead of developing a therapy that would alleviate symptoms, we focused on a solution that targets the root cause of the disease – the *Demodex* mite infestation itself.

We found a potential solution in lotilaner, a best-in-class, potent and selective anti-parasitic that was being utilized in veterinary medicine. We licensed lotilaner and developed a novel formulation of the molecule, suitable and safe for human use. Lotilaner had a favorable mite-killing profile, and we began our journey to test its effectiveness in potentially resolving *Demodex* blepharitis.

That discovery led to what is now XDEMVY (lotilaner ophthalmic solution) 0.25%, formerly known as TP-03, the first and only FDA-approved therapy for *Demodex* blepharitis.

Q: *Demodex* blepharitis is a common eyelid disease, yet many people have never heard of it. Could you tell us more about the disease?

A: *Demodex* blepharitis is caused by an overpopulation of *Demodex* mites, the most common ectoparasites found on humans. When present in small numbers, these mites go largely unnoticed. However, when a mite infestation occurs, it can lead to ocular irritation, inflammation, redness, itching and may impact a patient's daily activities. The symptoms of *Demodex* blepharitis often mirror those of ocular conditions like dry eye or allergies, so it is often undiagnosed. As a result, many patients may suffer with *Demodex* blepharitis for years.

Q: What is XDEMVY, how does it work, and why are you excited about its recent approval?

A: XDEMVY was approved by the FDA in July of this year for the treatment of *Demodex* blepharitis. The active ingredient in XDEMVY is lotilaner, which is designed to paralyze and eradicate *Demodex* mites by selectively inhibiting the mite's GABA-Cl channels.

The FDA approval is based on results from two randomized, multicenter, double-masked, vehicle-controlled studies (Saturn-1 and Saturn-2), designed to evaluate the safety and efficacy of XDEMVY in 833 patients, 415 of which received XDEMVY. Patients with *Demodex* blepharitis were randomized to either XDEMVY or vehicle at a 1:1 ratio and dosed twice daily in each eye over the course of 6 weeks. Efficacy was demonstrated by a significant improvement in eyelids (reduction of collarettes, the pathognomonic sign of the disease, to no more than 2 collarettes per upper lid) in each study by Day 43, with some patients seeing improvement as early as 2 weeks. Additionally, the endpoints of mite eradication (mite density of 0 mites per lash) and erythema cure (Grade 0) showed statistically significant improvement at Day 43 across both studies. In clinical trials, XDEMVY was generally safe and well tolerated. The most common ocular adverse reactions observed in the studies were instillation site stinging and burning which was reported in 10% of patients. Other ocular adverse reactions reported in less than 2% of patients were chalazion/hordeolum (stye) and punctate keratitis.

XDEMVY is the first and only FDA-approved treatment for *Demodex* blepharitis – this exciting milestone has the potential to help millions of patients with the disease and provides the opportunity for eye care providers to present a viable and effective solution to their patients.

Q: There's currently no established market for *Demodex* blepharitis. What is your approach to creating this new category in the eye care market, and why is it important?

A: We are extremely focused on elevating the importance of eyelid health and are thrilled to be the first to establish a market for *Demodex* blepharitis. The eyelids are the gateway to overall ocular health – they protect the eyes from external irritants, bacteria and keep the eyes lubricated.

Over the past year, we've been very focused on disease awareness and launched two impactful disease education

campaigns for eye care providers and consumers. *Demodex* blepharitis is easy to diagnose through a regular eye exam when an eye care provider asks a patient to "look down" during the exam. When a patient looks down, it allows the provider to examine the upper eyelash margin for the presence of collarettes. Collarettes are waxy, crusty build up (composed of mite waste and eggs) and are a sure sign of the disease.

The consumer disease awareness campaign provides tools and resources to encourage patients to visit and start a dialog with their eye care providers about *Demodex* blepharitis.

Q: What other disease areas is Tarsus focused on?

A: We have a rich and diverse pipeline, leveraging different formulations of lotilaner across other large disease areas for which there are unmet needs.

We are studying the potential safety and efficacy of TP-03 in Meibomian Gland Disease (MGD), another highly prevalent eyelid disease where *Demodex* mites may be implicated. MGD occurs when the meibomian glands do not secrete enough high-quality oil to effectively lubricate the surface of the eyes, resulting in dry eye, irritation, and fluctuating vision. We have a Phase 2a study underway for this disease.

We are also studying TP-05, a novel, investigative, oral therapeutic for the potential prevention of Lyme disease. Lyme disease is transmitted through *Borrelia burgdorferi* infection following the bite of a tick vector. Over 30 million Americans are at high or moderate risk of contracting Lyme disease and there are approximately 300,000 – 400,000 cases in the U.S. each year. TP-05 is designed to be an on-demand, long-acting prophylactic treatment that targets and eradicates ticks that transmit Lyme disease. TP-05 is currently being investigated in a Phase 2a trial. It is believed to be the only non-vaccine, drug-based, preventative therapeutic in development designed to kill ticks to potentially prevent Lyme disease transmission. There are currently no FDA-approved pharmacological prophylactic options for Lyme disease, which is the most common vector-borne disease in the United States, according to the CDC.

Finally, we are developing TP-04 for the treatment of papulopustular rosacea (PPR). Rosacea is a common inflammatory skin condition that affects more than 16 million people in the U.S. – PPR is estimated to occur in 18-28% of patients with rosacea, and can result in redness, swelling and/or pus-filled bumps. TP-04 is a topical, aqueous gel formulation of lotilaner designed to potentially treat PPR and eradicate *Demodex* mites, which have been reported as highly prevalent in the skin of patients with rosacea, including those with PPR, and may play a key role in triggering inflammatory responses associated with the disease. TP-04 is currently being studied in a Phase 2a clinical trial to evaluate safety, tolerability, and proof-of-activity.

Q: As Chief Operating Officer, what are your top priorities for the company over the next 2-3 years?

A: At Tarsus, our goal is to become a leading eye care company, helping to transform treatment for patients with serious diseases. As we work toward this goal, our top priorities are first to successfully commercialize XDEMVY and bring the first and only FDA-approved therapy for *Demodex* blepharitis to millions of patients and eye care providers. Second, we want to accelerate our pipeline and continue to develop potential therapies for Lyme disease prevention and rosacea. We are assessing all of our options to advance the development of these investigational therapies, including strategic partnerships. And finally, we want to continue to recruit and retain the best-in-class talent to maintain our award-winning culture that is focused on diversity, belonging, teamwork, and commitment to patients. ◆

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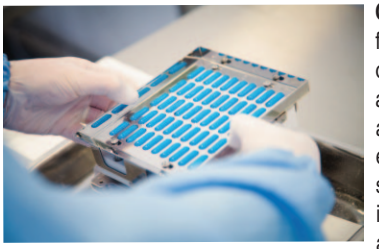

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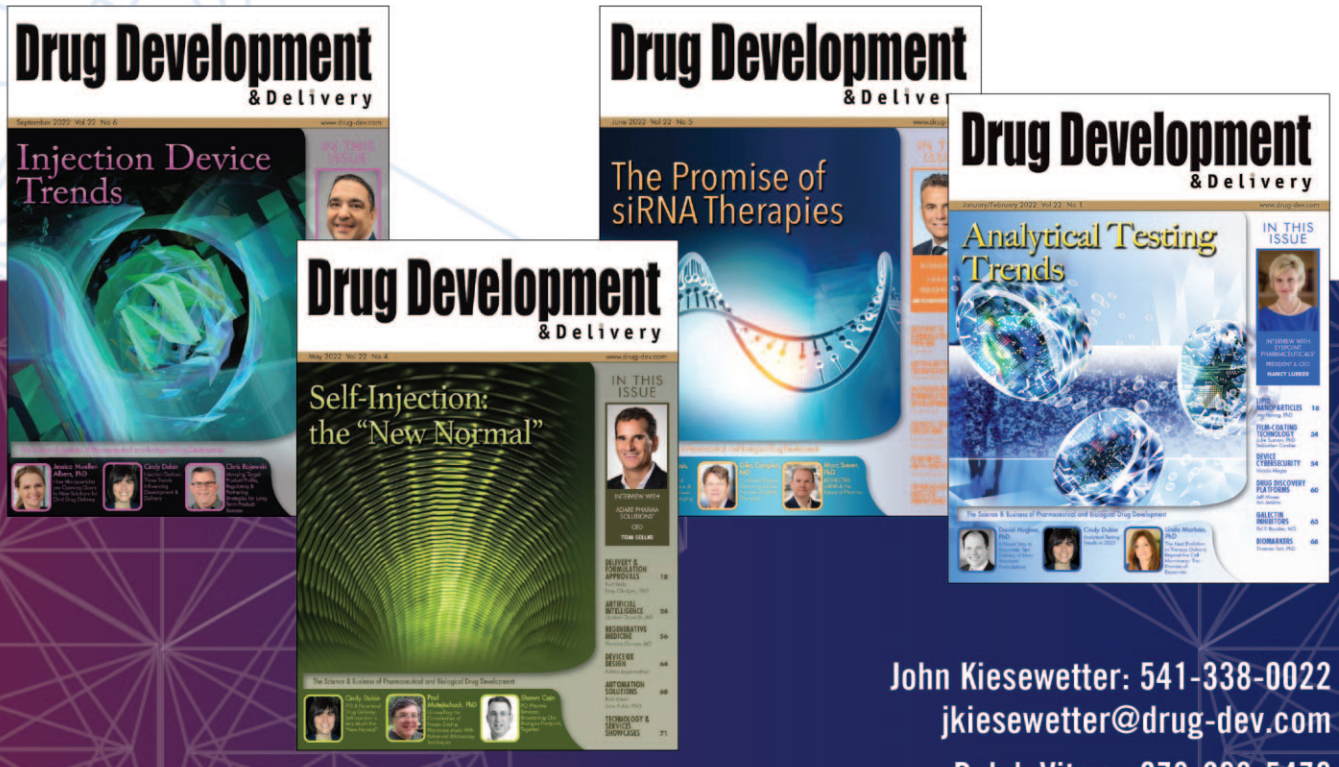

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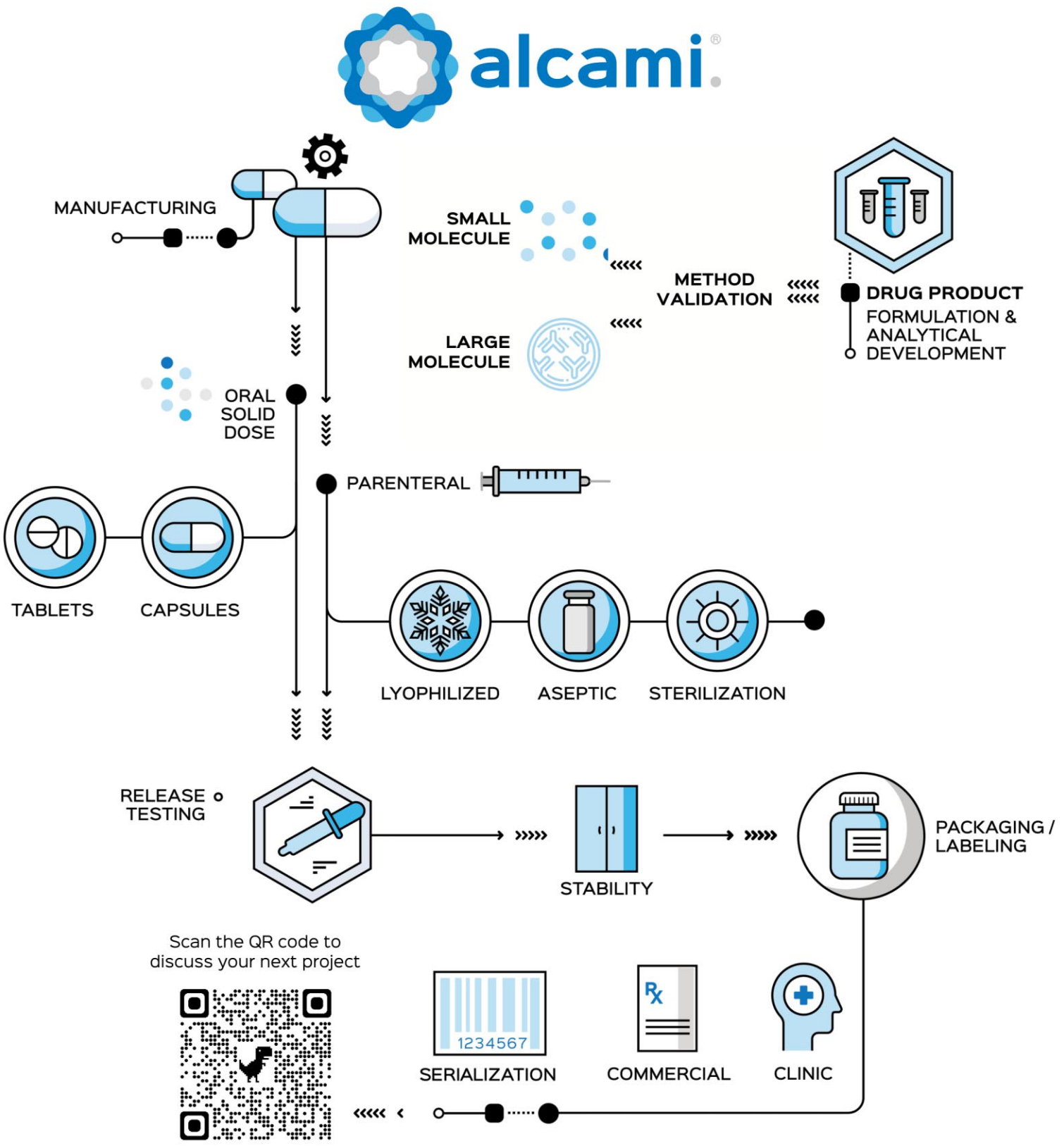

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