Drug Development & Delivery

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Self-Injection: the "New Normal"

The Science & Business of Pharmaceutical and Biological Drug Development

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ADARE PHARMA SOLUTIONS'

CEO

TOM SELLIG

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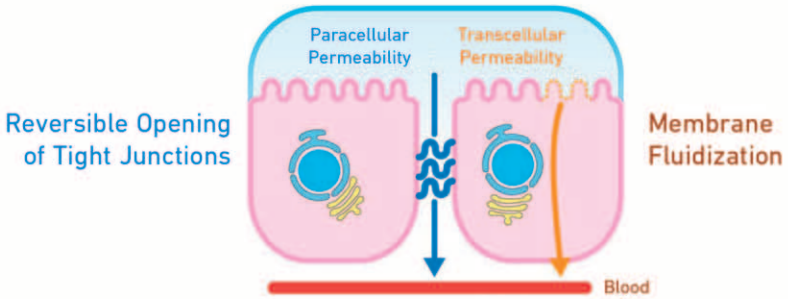

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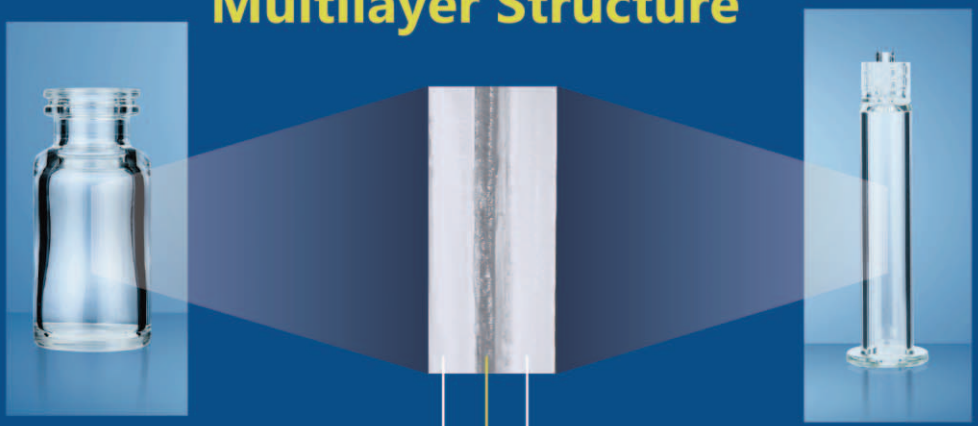

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Nest & Tub for Syringe

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INTO THE FUTURE... WITH CONFIDENCE AND CONSCIENCE

PFS & Parenteral Drug Delivery

"Covid-19 fast-tracked the healthcare industry's growing acceptance of patient self-injection, enabling patients to continue treatment outside of hospital environments and within outpatient facilities and home-care settings. And prefilled syringes represent the fastest-growing self-injection segment. In 2021, the global prefilled syringes market was valued at $5.8 billion. Overall, the market is expected to grow to $12.7 billion by 2028."

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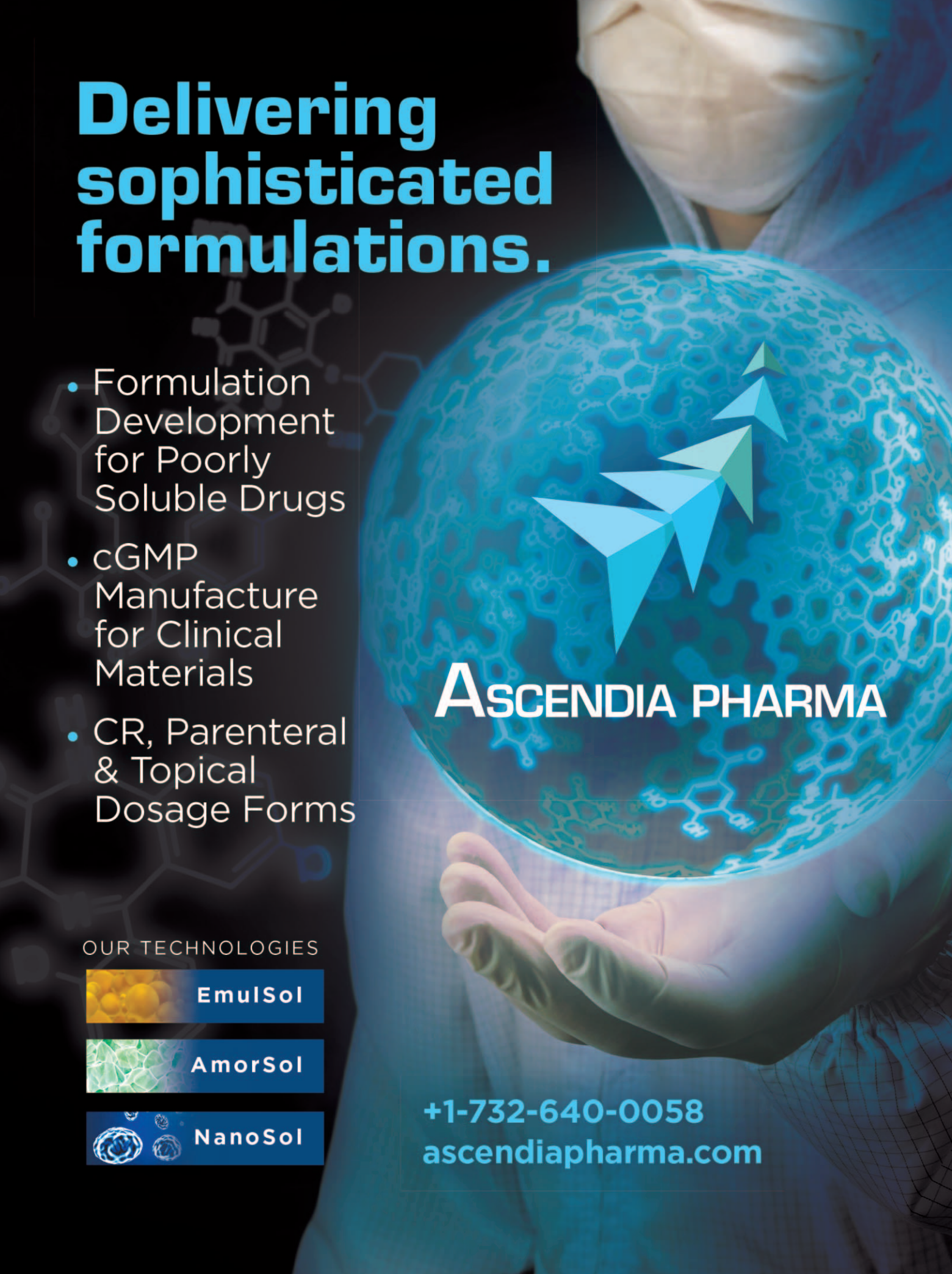
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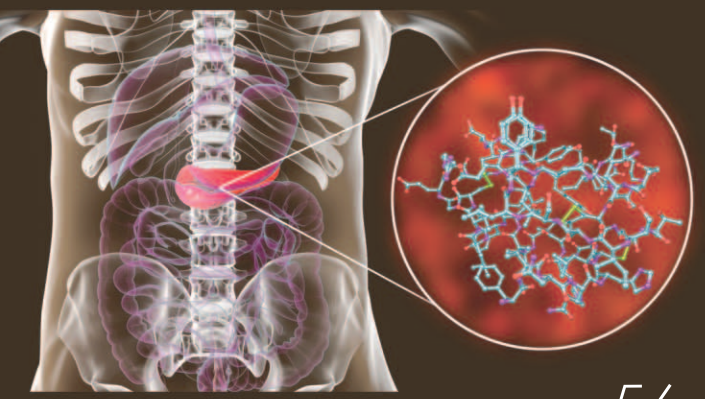
The Promise of Regenerative Medicine

"Regenerative medicine, led by advances in stem cell research and biomaterials, has the potential to restore the body's normal glucose regulatory system, offering promise in T1D treatment. These technologies, aimed at creating and implanting viable beta cells, could enable the tighter regulation of blood glucose levels. Once vascularized, these cells can monitor real-time glucose levels and rapidly adjust insulin delivery directly into the bloodstream versus patients injecting insulin into subcutaneous tissue, which can delay absorption."



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THE DIFFERENCE OF ONE DRUG DELIVERED

WITH A GLOBAL LEADER IN PREFILLABLE DELIVERY SYSTEMS. BD partners closely with leading pharmaceutical companies to support their success from drug development to launch and beyond. With a broad portfolio of innovative drug delivery systems, a global perspective and regulatory insights, a BD Medical–Pharmaceutical Systems team can partner with you to match the optimal solutions to your product. In addition to prefillable syringes, our technologies include self-injection systems, safety and shielding solutions—which we can customize and develop to meet your precise technical requirements and the demands of your business. You can also count on our depth of regulatory knowledge, product development, medical expertise and responsive support. Discover the confidence of working with the right partner. **Discover the difference of BD.**

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Caladrius Biosciences & Cend Therapeutics Announce Definitive Merger Agreement

Caladrius Biosciences, Inc. and Cend Therapeutics, Inc. recently announced the companies have entered into a definitive merger agreement under which Cend will merge with a wholly owned subsidiary of Caladrius in an all-stock approximate "merger of equals" transaction unanimously approved by the Boards of Directors of each company. Following closing, the combined company will be renamed Lisata Therapeutics, Inc. and will trade on the Nasdaq under the ticker symbol LSTA. The merger is currently expected to close in the third quarter of 2022 subject to the approval of Caladrius and Cend stockholders as well as the satisfaction of certain other customary closing conditions and applicable approvals.

Following the closing of the merger, Lisata is expected to advance CEND-1 as its lead product candidate in a variety of difficult to treat solid tumor applications, including pancreatic ductal adenocarcinoma (PDAC), where the product is being evaluated in ongoing Phase 1 and Phase 2 clinical studies with Cend and its partner in China, Qilu Pharmaceutical. CEND-1 is a proprietary cyclic peptide which undergoes protease mediated cleavage in the tumor microenvironment producing a C-end Rule or "CendR" peptide that potentiates transport across the tumor stroma and improves delivery of anticancer drugs to the tumor. Additional Phase 1b/2 PDAC clinical data is expected as early as 2023. Lisata also plans to initiate an additional trial in PDAC in combination with immunotherapy as well as a trial or trials exploring applications of CEND-1 in other difficult to treat solid tumors, such as hepatocellular, gastric and breast cancers along with additional therapeutic combinations. We see CEND-1's advancement as supported by compelling Phase 1b data previously presented at the 2020 European Society for Molecular Oncology (ESMO), which not only demonstrated favorable safety and tolerability, but importantly, the potential for marked improvement in treatment effectiveness in combination with standard of care drugs for PDAC. With its unique tumor-targeted, tissue penetrating technology, we believe that the CendR Platform holds the potential to enable more effective solid tumor treatment for a range of emerging treatment modalities, including RNA-based drugs. We believe that this could provide Lisata with additional partnering and product opportunities to benefit cancer patients and Lisata shareholders.

Under the terms of the definitive merger agreement, David J. Mazzo, PhD, current President and CEO of Caladrius will be the Chief Executive Officer of Lisata, David Slack, current President and CEO of Cend, will be Lisata's President and Chief Business Officer, and Kristen K. Buck, MD, current Executive Vice President of R&D and Chief Medical Officer, will continue in those roles with Lisata. Upon closing, shareholders of Cend will receive approximately 60.5 million shares of Caladrius common stock, subject to certain closing conditions, resulting in the shareholders of each company owning approximately 50% of the combined company.

Catalent to Invest $350 Million in Integrated Biologics Drug Substance & Drug Product Manufacturing

Catalent recently announced a multi-year $350-million investment at its facility in Bloomington, IN, to expand biologics drug substance and drug product manufacturing capabilities. The project will serve the industry's robust biologics pipeline across various modalities with new bioreactors, syringe filling lines, and additional lyophilization capacity, supported by quality control laboratories and complex automated packaging.

The expansion includes the installation of new 2,000-liter single-use bioreactors and expanded downstream processing capabilities for drug substance, with the versatility to meet customers' needs with batches of up to 4,000-liters using single-use technology, or 5,000-liters using existing stainless-steel bioreactors. Also included are new quality control laboratories and complex packaging space with additional high-speed, automated cartoning and auto-injector device assembly capabilities. It is envisioned that these new capabilities will be fully operational later this calendar year.

The site will also be adding to its drug product fill/finish capacity, with new syringe filling lines under barrier isolator technology and additional lyophilized vial capacity. When completed in 2024, the site's broad range of fill/finish offerings will provide great flexibility in dose form presentations and batch sizes to serve customers with everything from early- and late-stage development programs to high-volume commercial supply across various modalities. Altogether, these expansions are expected to add over 1,000 new jobs to Catalent's Bloomington workforce in the coming years.

"We continue to see strong growth in demand for biologics development and manufacturing with a deep pipeline across multiple indications," commented Mike Riley, President of Biotherapeutics at Catalent. "These investments will enable us to expand our flagship Bloomington facility and extend our leadership as one of the largest and most comprehensive global centers for integrated manufacturing capabilities. The site offers highly flexible and scalable solutions to companies developing new biological drugs, vaccines, RNA therapies, and other innovative treatments for patients around the world."

This expansion follows a series of recent investments in Catalent Biologics' global network, including the modernization of its fill/finish and packaging facility in Limoges, France, and the acquisition of a new biologics development and manufacturing facility near Oxford, UK.

Catalent Biologics is a global leader in development, manufacturing and analytical services for new biological entities, cell and gene therapies, biosimilars, sterile injectables, and antibody-drug conjugates. With over 30 years of proven expertise,
Catalent Biologics has worked with more than 600 mAbs and more than 80 proteins, produced 16 biopharmaceutical drugs using GPEx cell line development technology, and manufactured more than 45 commercially approved products. For more information, visit biologics.catalent.com.

Catalent is the global leader in enabling pharma, biotech, and consumer health partners to optimize product development, launch, and full life-cycle supply for patients around the world. With broad and deep scale and expertise in development sciences, delivery technologies, and multi-modality manufacturing, Catalent is a preferred industry partner for personalized medicines, consumer health brand extensions, and blockbuster drugs. Catalent helps accelerate over 1,000 partner programs and launch over 150 new products every year.

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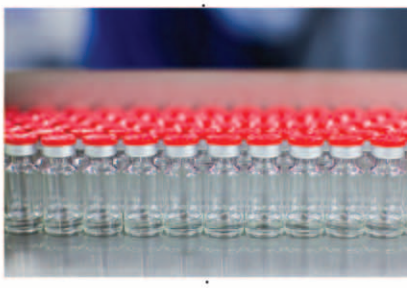

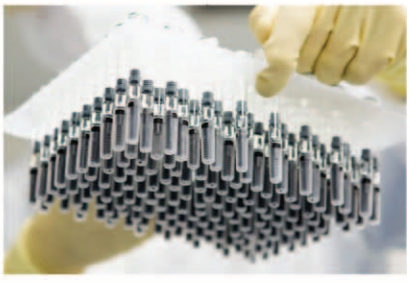

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SOTIO Initiates CLAUDIO-01 Trial With Antibody-Drug Conjugate SOT102 in Patients With Gastric & Pancreatic Cancer

SOTIO Biotech recently announced it has dosed the first patient in its Phase 1/2 CLAUDIO-01 trial of SOT102 in patients with gastric and pancreatic cancer. SOT102 is the lead program of SOTIO's growing ADC pipeline built on multiple platforms.

"Antibody-drug conjugates constitute one of the most exciting drug classes in oncology," said Radek Spisek, MD, PhD, Chief Executive Officer of SOTIO. "The careful design of SOT102, including the use of NBE-Therapeutics' ADC platform is aimed to provide an efficacious and safe treatment option for patients with CLDN18.2 cancers."

The Phase 1/2 CLAUDIO-01 trial (EudraCT number: 2021-005873-25) is a first in human, open label, multicenter clinical trial to assess the safety and preliminary efficacy of SOT102 in monotherapy and in combination with established standard of care therapies (SoC). The trial will enroll up to 109 patients with gastric adenocarcinoma or adenocarcinoma of the gastroesophageal junction (GEJ) and pancreatic adenocarcinoma across sites in Belgium, the Czech Republic, France, Spain, and the US. The first patient was dosed at the Masaryk Memorial Cancer Institute, Brno, Czech Republic, under the supervision of Radka Obermannova, MD, PhD, principal investigator.

Josep Tabernero, MD, PhD, Head of Medical Oncology at Vall d'Hebron University Hospital and coordinating investigator of the trial, added "CLDN18.2 is a promising target in gastric and pancreatic cancer due to its prevalent expression in cancers of the gastrointestinal tract. Based on its preclinical data SOT102 represents a potentially safer and more effective treatment option for targeting the CLDN18.2 protein in gastric and pancreatic cancers. The initiation of this clinical trial is major milestone in studying its potential benefit for these patients."

SOT102 is a CLDN18.2 targeting antibody-drug conjugate based on a proprietary, highly specific monoclonal antibody conjugated to a potent cytotoxic drug molecule and is being developed in collaboration with NBE-Therapeutics. Preclinical data from studies of SOT102 have demonstrated potent anti-tumor efficacy in vitro and in vivo and, due to NBE's proprietary site-specific sortase mediated antibody coupling (SMAC) conjugation platform.

SOTIO Biotech is shaping the future of cancer immunotherapies by translating compelling science into patient benefit. The robust SOTIO clinical pipeline includes a differentiated superagonist of the attractive immuno-oncology target IL-15, SOT101, currently being tested in Phase 2 clinical trials. SOT102, a next-generation Claudin18.2-targeted antibody-drug conjugate (ADCs) has just entered clinical phase. Two programs will enter Phase 1 clinical testing within 2022, including SOT201, an IL-15-based immunocytokine and BOXR1030, a GPC3-targeted CAR-T based on proprietary technology designed to improve on the efficacy of CAR T therapies in the tumor microenvironment. SOTIO is a member of the PPF Group. For more information, visit www.sotio.com.

First European Union Patient Dosed With 177Lu-PNT2002 in the Phase 3 SPLASH Trial

POINT Biopharma Global Inc. recently announced the first patient in the European Union (EU) has been dosed in the Phase 3 SPLASH trial (NCT04647526). The SPLASH trial is investigating the use of 177Lu-PNT2002, a PSMA-targeted radioligand, in pre-chemotherapy metastatic castration-resistant prostate cancer (mCRPC), with entry criteria including a positive PSMA-PET scan with either 68Ga-PSMA-11 or 18F-DCFPyL.

The SPLASH trial began randomization in North America in September 2021, and a total of 37 trial sites across North America and Europe are currently enrolling patients. Site activations in remaining jurisdictions continue to further accelerate trial recruitment. The company continues to expect to report top line data from SPLASH mid-2023.

"I'm pleased with our team's consistent execution of the SPLASH trial," said Dr. Joe McCann, CEO of POINT Biopharma. "In 2 years, we've gone from a pre-IND meeting with the FDA to dosing patients in multiple countries, and I'm proud of our team for realizing this achievement. We remain on track to complete recruitment by the end of this year, and to disclose efficacy and safety data from the 27-patient lead-in in the second half of 2022."

In February 2022, the company announced publication of the first data from the SPLASH trial, dosimetry results from the lead-in cohort. The findings presented by Dr. Jean-Mathieu Beauregard concluded that "PNT2002 has a favorable and safe dosimetry profile in the patient population and dose regimen being studied." To provide additional context on interpreting dosimetry, the company also hosted an investor education event titled Introduction to Dosimetry for Radiopharmaceuticals shortly after the release of the data. The 30-minute educational webinar was led by Dr. Ana Kiess, MD, PhD, Assistant Professor of Radiation Oncology and Molecular Radiation Sciences at Johns Hopkins Hospital, and provides more context into interpreting dosimetry results. A replay of the webinar and the slides are available to download at https://hub.pointbiopharma.com/dosimetry.

POINT Biopharma Global Inc. is a globally focused radiopharmaceutical company building a platform for the clinical development and commercialization of radioligands that fight cancer. POINT is transforming precision medicine by combining a portfolio of best-in-class radiopharmaceutical assets, a seasoned management team, an industry-leading pipeline, in-house manufacturing capabilities, and secured supply for rare medical isotopes like actinium-225 and lutetium-177. For more information, visit https://www.pointbiopharma.com/. Information about POINT Biopharma Global Inc.'s Phase 3 SPLASH trial for metastatic castrate resistant prostate cancer (mCRPC) patients can be found at https://www.splashtrial.com/.

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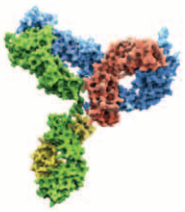
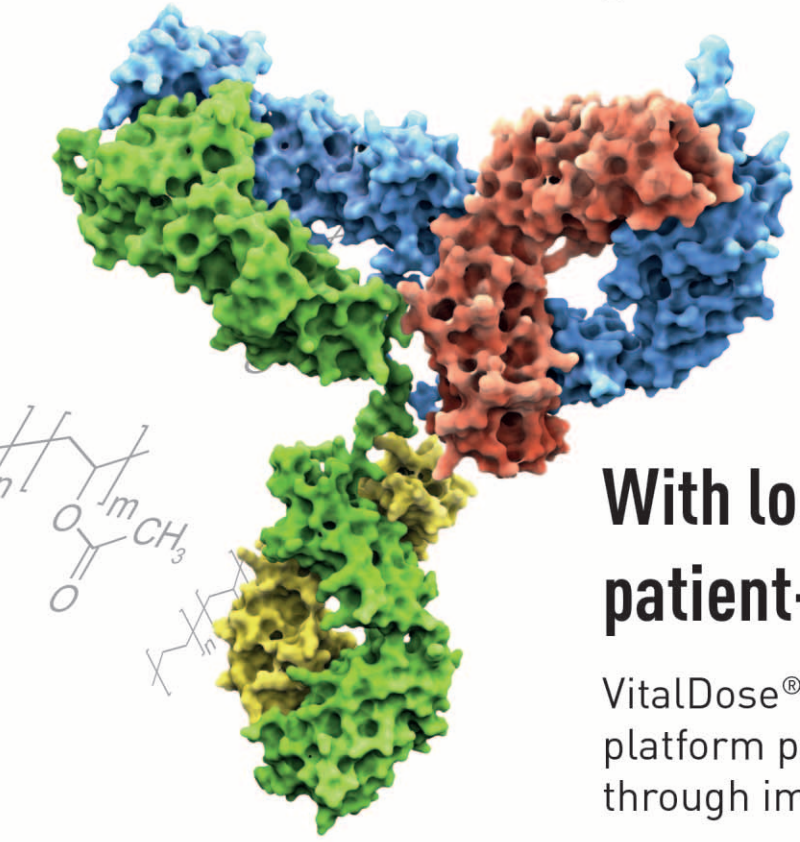
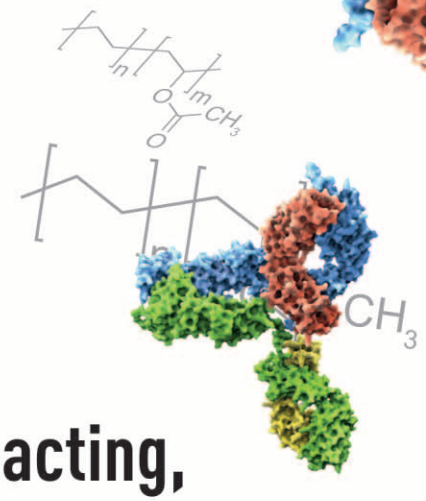
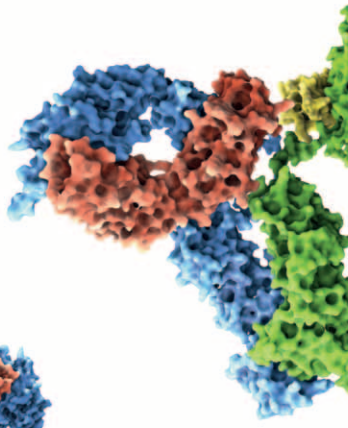


Sustained Drug Delivery







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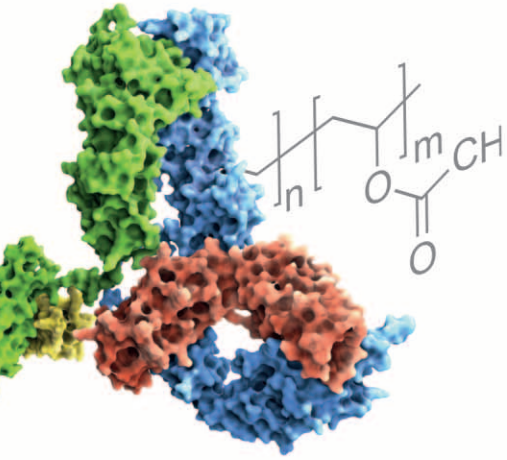

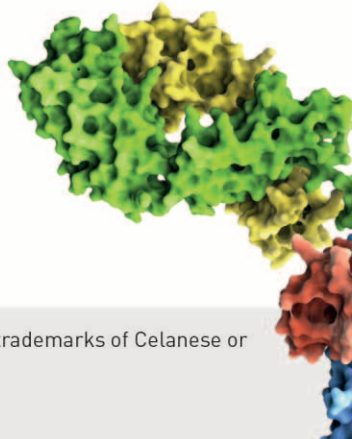

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Sol-Gel Technologies & Galderma Announce FDA Approves First Topical Rosacea Treatment With Microencapsulated BPO

Sol-Gel Technologies, Ltd. recently announced the Food and Drug Administration (FDA) approval of its drug product, EPSOLAY, a proprietary cream formulation of benzoyl peroxide, 5%, for the treatment of inflammatory lesions of rosacea in adults.

The benzoyl peroxide in EPSOLAY is encapsulated within silica-based patented microcapsules. The silica-based shell is designed to slowly release benzoyl peroxide over time to provide a favorable efficacy and safety profile. The approval of EPSOLAY is supported by data from two positive, identical Phase 3 randomized, double-blind, multicenter, 12-week, clinical trials that evaluated the safety and efficacy of EPSOLAY compared to vehicle in people with inflammatory lesions of rosacea (N = 733). The co-primary endpoints in both trials were the proportion of subjects with treatment success and the absolute change from baseline in lesion counts at Week 12. EPSOLAY was more effective than vehicle cream on the co-primary efficacy endpoints starting from 4 weeks of treatment in both trials. With EPSOLAY treatment, inflammatory lesions of rosacea were reduced by nearly 70% by the end of both 12-week trials vs. 38-46% with vehicle. Nearly 50% of subjects were 'clear' (IGA=0) or 'almost clear' (IGA=1) at 12 weeks vs. 38-46% with placebo. Post-hoc analysis of lesion count and IGA success at Week 2 confirmed a significantly greater treatment effect for EPSOLAY relative to vehicle as early as Week 2. In the open-label extension, 73% of subjects were 'clear' (IGA=0) or 'almost clear' (IGA=1) at 52 weeks (N = 547).

Sol-Gel has granted to Galderma Holding SA (Galderma) the exclusive rights to commercialize EPSOLAY in the US. Founded in 1981, Galderma is the world's largest independent dermatology company.

"Having EPSOLAY approved by the FDA is a watershed moment for the 16 million people in the US suffering from rosacea," stated Alon Seri-Levy, PhD, Chief Executive Officer of Sol-Gel. "Based on the robust clinical data, we believe that EPSOLAY has the potential to change the treatment landscape. We are proud to have Galderma as our partner to launch this drug since Galderma has an unparalleled track record of introducing innovative drugs in the US's rosacea market."

"Galderma is committed to delivering innovation in dermatology so that healthcare professionals and their patients have the products they need," said Baldo Scassellati Sforzolini, MD, PhD, Global Head of Research & Development at Galderma. "People with rosacea experience a significant burden of disease with diminished quality of life and the approval of EPSOLAY represents an important advancement for those who are living with rosacea. We are pleased to be able to launch EPSOLAY and look forward to bringing this new treatment option to the US."

EPSOLAY is a topical cream containing benzoyl peroxide, 5%, for the treatment of inflammatory lesions of rosacea in adults. EPSOLAY utilizes a proprietary technology to encapsulate benzoyl peroxide within silica-based microcapsules to create a barrier between the medication and the skin. The silica-based shell is designed to slowly release benzoyl peroxide over time to provide a favorable efficacy and safety profile. EPSOLAY is covered by granted patents until 2040.

Blacktrace Launches Particle Works – The New Dedicated Particle Engineering Brand

Blacktrace Holdings Ltd – a world leader in Productizing Science – recently announce the launch of Particle Works, a spin out of Dolomite Microfluidics. The official launch of this new brand will took place at the LNP Formulation and Process Development Summit in Boston, MA, April 12-14, 2022.

Particle Works' game-changing particle engineering platforms are set to revolutionise the way customers discover, develop and scale-up particle production for a wide range of applications. The brand draws on Blacktrace Holdings' 20+ years of experience in particle engineering and microfluidic technology to offer novel systems for the consistent and reliable generation of various particle types for use in the medical, biotechnology, and materials science industries.

Previously, nanoparticles – such as liposomes, lipid nanoparticles (LNPs), and polymer-based nanoparticles – have been produced using batch methods that are inconsistent and difficult to control, risking damage to encapsulated products and leading to polydisperse particles to produce variable in vivo results. Particle Works will solve this challenge by using proven and reliable microfluidic technologies to create pioneering systems capable of consistent and tuneable particle generation. This will enable the manufacturing process to be more stable and efficient, with a lower chance of particle damage, further reducing time of development cycles compared to traditional batch methods. The brand will initially focus on enhancing drug encapsulation and vaccine delivery, opening previously inaccessible extremely performant and precision solutions to its customers.

Lee Jeffries, Managing Director of Particle Works, explained "As leaders in the field of particle technology, we understand the needs of our customers, and Particle Works is the direct result of the growing demand for reliable and scalable solutions for nanoparticle production. From formulation, screening, and process optimization to scale-up manufacturing, Particle Works will provide scientists with innovative and automated platforms to speed up their processes, enabling customers to produce nanoparticles with unrivalled precision, consistency and control. This will help to minimize sample use and shorten timelines from discovery to manufacture."

Particle Works combines a strong heritage in engineering with scientific knowledge, microfluidic expertise and in-house chip fabrication. We are dedicated to designing and building state-of-the-art particle engineering platforms, paving the way to particle perfection. Our technology is used in a wide range of applications, including the production of nanoparticle-based vaccines, medicines, and therapeutics. Building on the tried and tested technology of Dolomite Microfluidics, Particle Works' platforms enable scientists to formulate particles faster, ensuring they are ready for their next breakthrough and the scale up of discoveries. We have been at the forefront of this rapidly changing science, listening and adapting as our customers' needs have evolved. With Particle Works, we bring you a focused brand where together we can unlock the true power of particles.

Particle Works is part of Blacktrace Holdings Limited – a world leader in Productizing Science – and is based in Royston (near Cambridge) UK. We have offices in the US, Japan, and Vietnam, and worldwide distributors offering technical assistance and support.

Symeres Acquires Organix, Adding Lipids Expertise & Strategic Foothold in the US

Symeres recently announced the acquisition of Organix Inc., a US-based specialized organic chemistry services provider with a focus on lipids. As the majority shareholder in Symeres, Keensight Capital has worked together with the management team of the two companies to facilitate this business combination.

Organix, based in the Boston area (Massachusetts), is a provider of high-quality organic chemistry services dedicated to the discovery and preclinical stage of the drug discovery value chain. Its revenue is mainly generated from the sale of specialized and complex organic chemistry research services to biopharma clients. Organix is currently generating over $10 million of revenues, from a base of c.45 employees, of which the majority have PhDs in chemistry.

Symeres and Organix are highly complementary, and the combination unlocks significant strategic value. Organix brings a high-quality presence in the US market, where Symeres generates nearly 50% of its revenues. Organix broadens Symeres' drug discovery offering into the fast-growing lipids market, addressing mRNA therapeutics and vaccines. Organix's impressive client list includes some of the world's leading biopharma companies, including many based in the Boston biopharma community.

Symeres is one of the largest European small molecule CRO & CDMOs, providing R&D services from preclinical drug discovery to Phase 1 and 2 clinical stage drug development and manufacturing, to major pharmaceutical and biotechnology companies around the globe. Its highly specialized services include integrated small molecule optimization efforts, complex synthetic chemistry, route scouting & API synthesis up to GMP production, solid state chemistry and ADME-Tox services.

Symeres, headquartered in the Netherlands, employs over 500 people, many of whom are PhD scientists, operating in the Netherlands, the Czech Republic, and Nordics, along with an existing business development office in the Boston area. Over several decades, the company has enjoyed a strong growth trajectory, with revenues rising organically at a double-digit rate per annum, further complemented by strategic M&A. Proforma for the integration of Organix, the group expects to reach c.€90 million in revenues.

Dr. Anu Mahadevan, CEO of Organix, said "We are proud to become part of the Symeres family where we have found a trusted partner that shares our values and business philosophy of strong customer focus. The added expertise that the deal brings will allow Organix to better serve our clients by providing additional access to state-of-the-art cGMP services. We look forward to being a part of this innovative and science-driven organization."

Dr. Eelco Ebbers, co-founder and CEO of Symeres, added "We are pleased to welcome Organix into the Symeres Group. Organix is widely known as a highly innovative and expert organic chemistry services provider that solves complex projects for top tier clients globally. Joining forces represents a fantastic opportunity for Symeres to expand our drug discovery capability offering and will provide an exceptional foothold into the US market."

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2021 Global Drug Delivery & Formulation REPORT

Part Two of a Three-Part Series

Part 1: A Review of 2021 Product Approvals

Part 2: Notable Drug Delivery and Formulation Product Approvals and Technologies of 2021

Part 3: Drug Delivery and Formulation Pipeline Trends

By: Kurt Sedo, Vice President Operations, and Esay Okutgen, PhD, Director Drug Delivery, PharmaCircle LLC

Introduction

It appears the industry's attention has moved on from gene therapy and mRNA. Despite remarkable commercial and therapeutic successes, both platforms are searching for their "second acts." In 2021, attention returned to drug delivery- and formulation-based products and technologies applicable to larger patient populations and more diverse indications.

The notable approved drug delivery- and formulation-enabled and approved products of 2021 include Ascendis' weekly human growth hormone product Skytrofa, and Janssen's 6-month formulation of paliperidone aptly named Invega Hafyera, both variations on earlier themes. The list also includes a trio of products targeted to ophthalmic indications, Oyster Point's Tyrvaya, J&J's ACUVUE Theravision, and Genentech's Susvimo, the latter representing first approvals for their novel delivery platforms. ViiV's Cabenuva Kit rounds out the list delivering sustained-release depot therapy to the HIV patient population.

Platform technology best describes the notable technologies of 2021. Included are Genentech's Port Delivery System that underlies its Susvimo product, a notable product of 2021, providing important dosing options for their well-validated AMD treatment ranibizumab. Medicago's Virus Like Particles (VLP), with the approval of their first product, a COVID-19 vaccine, demonstrates the prospects of the platform for additional vaccines and therapeutics. Ionis's LICA technology further refines the potential of oligonucleotides by providing greater selectivity and improved efficiency. The Denali Transport Vehicle (TV) platform, currently at a Phase 2 stage of development, includes four separate technologies intended to provide facilitated crossing of the blood-brain barrier by antibody, enzyme, oligonucleotide, and protein therapeutics. At an earlier stage of development, LaGalli's MedRing platform integrates a pump, liquid drug reservoir, and electronics to permit a connected "intelligent" vaginal ring delivery system for both therapeutic and diagnostic applications.

The stars of the past couple of years, gene and cell therapy technologies, as well as mRNA delivery platforms, are struggling to move beyond a few highly specialized therapeutic uses. Gene therapy is facing safety and durability concerns while mRNA searches for validation outside of the field of vaccines. Both platforms continue to earn significant industry interest as evidenced by transaction activity and litigation related to the underlying intellectual property.

Even in an age of disruption, the pharmaceutical industry continues to demonstrate remarkable resilience and innovation. COVID too will pass.

Notable Drug Delivery and Formulation Products of 2021

Skytrofa (Ascendis Pharma)

Active: lonapegsomatropin-tcgd
Molecule Type: PEG-protein
Indication: Growth Failure - Pediatric
Delivery Route: Injection, Subcutaneous
Dosage Form: Lyophilized Powder, Dual Chamber Cartridge Technology
DD Category: Conjugates, PEG Polymer
Dosing: Weekly
First Approval: 2021-08-25 (USA)
Technology: TransPEG/TransCon
Owner: Ascendis Pharma

Development Summary

Development started in 2009 with the initiation of a pharmacokinetics study. Phase 3 trials were initiated in 2016 followed by filing with the FDA in June of 2020. First-in-human to approval took 10.7 years.

Platform/Technology/Formulation Summary

The TransPEG/TransCon technology application to Skytrofa involves the attachment of a 40kDa mPEG to the human growth hormone (hGH) molecule with a proprietary TransCon linker. This "transient" linker releases the parent hGH molecule and produces a linear IGF-1 response peaking about 2 days post dosing with average IGF-1 levels in the normal range for the week. Skytrofa uses the Vetter Dual Chamber Cartridge system in conjunction with of the Skytrofa Autoinjector developed in partnership with Phillips Medisize. The rechargeable and reusable injection device offers wireless connectivity and mixes the medication, easing the burden of self-injection for patients.

Reflections

In addition to providing improved convenience with weekly injections, Skytrofa provides increased Annualized Height Velocity of about 1 cm/year (0.2-1.5) versus daily injections of hGH. This improved growth comes at the expense of a slight increase in generally mild adverse events. The experience with Skytrofa seems to parallel that of the PEG-interferons used for the treatment of Hepatitis C in which moving from multiple doses per week to a single weekly injection consistently improves therapeutic outcomes. Whether there is a physiological reason for the improvements, or it is the result of better compliance, there is strong evidence to support the therapeutic value of longer-acting pharmaceuticals with extended dosing intervals.

Invega Hafyera (Janssen Pharmaceuticals)

Active: paliperidone palmitate
Molecule Type: Small Molecule
Indication: Adult Schizophrenia
Delivery Route: Injection, Intramuscular
Dosage Form: Injection Suspension, Prefilled Syringe
DD Category: Biodegradable Gel/Suspension
Dosing: Every 6 Months
First Approval: 2021-08-30 (USA)
Technology: NanoCrystal
Technology Owner: Alkermes

Development Summary

Hafyera was submitted to the FDA in October 2020 as a supplement to the Invega Trinza (3-month paliperidone palmitate) and approved 10 months later. The earliest human trial found for Invega Hafyera is a November 2017 efficacy trial comparing it with the approved 1-month and 3-month formulations of paliperidone, suggesting a 3.7-year interval between first human trial and approval.

Platform/Technology/Formulation Summary

A look at the available information for Invega Hafyera suggests it is a larger volume version of Invega Trinza. Both formulations report 312-mg/ml concentrations of paliperidone and similar mg per ml excipient amounts with varying dosage volumes. Invega Sustenna, the 1-month formulation, has a 156-mg/ml concentration. The excipients include Polyethylene Glycol 4000 and Polysorbate 20.

Reflections

The technology associated with Invega Hafyera is at this point unremarkable. What is remarkable is the Janssen lifecycle management for their Invega franchise, which for almost 2 decades has captured significant revenue with its Invega portfolio, over $4 billion in 2021 despite loss of exclusivity for the parent molecule. Invega Hafyera represents a development bargain essentially requiring little more than a pair of efficacy-confirming clinical trials and investments in fill and finish upgrades and validation.

Tyrvaya (Oyster Point Pharma)

Active: varenicline
Molecule Type: Small Molecule
Indication: Dry Eye
Delivery Route: Nasal
Dosage Form: Nose Spray
DD Category: Nasal Spray Pumps/Devices
Dosing: Twice Daily
First Approval: 2021-08-30 (USA)
Technology: NanoCrystal
Technology Owner: Alkermes

Development Summary

US development started in June 2018 with an announcement the FDA had cleared the company's IND for Tyrvaya. This was followed by Phase 2 and Phase 3 trials, an FDA submission in December 2020, and approval in October 2021. The rather compact clinical development and approval time of 3.3 years is notable for an active previously approved in an oral formulation to assist smoking cessation.

Platform/Technology/Formulation Summary

Tyrvaya represents the first approval for Aptar's CPS Spray Pump, a preservative-free nasal delivery platform for the treatment of Dry Eye. The formulation itself is simple, consisting of water, sodium phosphate, and buffer solution

Reflections

The challenge of administering drops to the eye cannot be overestimated, particularly in the target population of individuals who tend to be older and/or experiencing compromising medical conditions. Tyrvaya represents a practical and elegant drug delivery-based solution for a too common therapeutic challenge. Notable as well is the efficient use of drug delivery to repurpose an active for a whole new therapeutic indication.

ACUVUE Theravision (Johnson & Johnson Vision Care)

Active: ketotifen
Molecule Type: Small Molecule
Indication: Ocular Itch (allergic conjunctivitis)
Delivery Route: Contact Lens
Dosage Form: Ophthalmic Insert
DD Category: Ocular Lenses/Inserts
Dosing: Daily
Fast Approval: 2021-03-24 (Japan)
Delivery Route: Contact Lens
Technology: J&J Drug Eluting Contact Lens
Technology Owner: J&J Vision Care

Development Summary

The earliest reported clinical trial of ACUVUE Theravision is a Phase 3 trial initiated December 2017. It is likely that pharmacokinetic and safety studies were conducted earlier. Underlying patents to the technology have priority dates of 2012. The product was approved February 2022 in the US.

Platform/Technology/Formulation Summary

The antihistamine (ketotifen)-releasing contact lenses are corrected disposable lenses worn daily. The lens material, etafilcon A, is a copolymer of 2-hydroxyethyl methacrylate and methacrylic acid cross-linked with 1, 1, 1-trimethylol propane trimethacrylate and ethylene glycol dimethacrylate. The lenses are tinted blue using blue 2-hydroxyethyl methacrylate to make the lenses more visible for handling.

Reflections

The concept of using contact lenses, corrected or not, provides a compelling platform for the continuous delivery of any number of drugs that require the application of drops and possibly injection. While ACUVUE Theravision is limited to the treatment of ocular itch associated with allergic conjunctivitis, and daily replacement of the contact lenses, the application of the technology to other indications and actives is obvious. The limitation of the technology is that it requires the patient to apply the contact lens daily, something not necessarily appealing to patients not currently using contact lenses. A major technical accomplishment is the stabilizing of the drug in the contact lens to prevent leaching.

Cabenuva Kit (ViiV Healthcare)

Active: cabotegravir, rilpivirine
Molecule Type: Small Molecule (both)
Indication: HIV-1 Infection
Delivery Route: Injection, Intramuscular
Dosage Form: Injection Suspension

DD Category: NP Milling, Biodegradable Gel/Suspension
Dosing: Monthly
First Approval: 2020-03-18 (Canada)
Delivery Route: Contact Lens
Technology: NanoCrystal
Technology Owner: Alkermes

Development Summary

This product represents a new combination incorporating a new active, cabotegravir. The earliest human trials for cabotegravir date back to 2008. First human trials of a combination of the two actives date to 2011. The first trial of the long-acting injectables dates to May 2012. The application for FDA approval was filed April 2019.

Platform/Technology/Formulation Summary

The "kit" incorporates separate vials of cabotegravir and rilpivirine. Both suspensions use NanoCrystal nanoparticle milling technology. The cabotegravir formulation uses Polysorbate 20 and Polyethylene Glycol 3350, while the rilpivirine formulation uses a Poloxamer base.

Reflections

Cabenuva Kit is similar to other long-acting agents in which there are therapeutic benefits to maintaining consistent and adequate therapeutic serum levels. Patients prescribed the Cabenuva Kit are dosed orally for about a month before the monthly injections are initiated. Clinicians are increasingly appreciating the benefits of longer-acting injectables for conditions in which compliance can be a concern and patient initiated "drug holidays" can have serious consequences. (In March 2022 the FDA approved the use of Cabenuva Kit without the need for an oral dosing lead-in and extended dosing to two months.

Susvimo (Genentech)

Active: anibizumab
Molecule Type: anibizumab
Indication: Wet Acute Macular Degeneration
Delivery Route: Injection, Intravitreal
Dosage Form: Implant

DD Category: Ocular Implants / Rods / Microcapsules
Dosing: Every 6 Months
First Approval: 2021-10-22 (USA)
Technology: Port Delivery System
Technology Owner: ForSight Vision4 (Roche)

Development Summary

The earliest clinical trials for the ranibizumab using the Port Delivery System (PDS) date to 2010. Roche acquired ForSight Vision4 in 2017 and filed for approval of Susvimo with the FDA in April 2021, receiving Priority Review. The overall clinical and approval time for Susvimo totaled a little more than 11 years.

Platform/Technology/Formulation Summary

The Port Delivery System (PDS) is a novel refillable eye implant, approximately the size of a grain of rice, providing controlled delivery to the vitreous humor over months or years. Following initial implantation, refills can be performed in the office as needed, as used for standard-of-care intravitreal injections. The PDS implant is made of non-biodegradable materials. The aqueous drug formulation uses Polysorbate 20 and histidine.

Reflections

With an aging population and high patient expectations for continued functional performance, companies are finding therapeutic and commercial opportunity with novel of ophthalmic drugs and delivery methods. Even presbyopia has received attention with a recent pharmaceutical approval. Susvimo validates the possibilities for the treatment of other eye diseases with the PDS and similar implantable systems to provide for better compliance and outcomes.

Notable Drug Delivery and Formulation Technologies of 2021

Technology: Port Delivery System
Most Advanced Stage: Marketed
Technology Category: Ocular Implant
Company: ForSight VISION4 Roche/Genentech
Notable Pipeline: Marketed - Susvimo (ranibizumab)
Notable: Refillable ocular implant that extends dosing intervals of macromolecules for up to six months

Technology Summary: The Port Delivery System (PDS) is a novel refillable eye implant, approximately the size of a grain of rice, which continuously delivers drugs over months or years into the vitreous humor in a controlled manner. Following initial implantation, refills can be performed in the office similar to that used for standard-of-care intravitreal injections. Susvimo uses a customized Polysorbate 20 and histidine formulation of ranibizumab distinct from the intravitreal injection marketed as Lucentis. The PDS system includes implant, injector and implant inserter.

Technology: Medicago Virus Like Particles (VLP) Technology
Most Advanced Stage: Approved
Technology Category: Virus Like Particles
Company: Medicago/Mitsubishi Tanabe Pharma
Notable Pipeline: Approved - Covifenz (COVID-19 Vaccine)
Notable: First approved plant based Virus Like Particle technology product

Technology Summary: Medicago's plant-derived vaccine development technology platform uses tobacco-related plants indigenous to Australia (Nicotiana benthamiana) as bioreactors to produce non-infectious Virus Like Particles (VLP) that mimic the target virus. The plants are not genetically modified. Plant-specific bacterial vectors containing antigenic viral gene sequences transfect the plants, which produces VLPs for 4-6 days. The Covifenz injectable emulsion vaccine formulation uses a wide variety of excipients, including 1018 ISS, AS03, Polysorbate 80, Squalene, and Alpha tocopherol as adjuvants.

Technology: LICA Technology
Most Advanced Stage: Phase 3
Technology Category: Conjugates, Carbohydrate; Receptor/Carrier, Liver Targeting
Company: Ionis Pharmaceuticals
Notable Pipeline: Phase 3 - Pelacarsen (Apo(a)), Eplontersen (ATTR), Olezarsen (ApoC-III), Donidalorsen (Hereditary Angioedema)
Notable: Increased cell and tissue selectivity with increased potency

Technology Summary: LICA, or Ligand Conjugated Antisense, involves the attachment of ligands that bind with targeted receptors on the surfaces of cells. LICA permits effective delivery of antisense drugs with specificity to cell types expressing these receptors. The specificity provides for a 20- to over 30-fold increase in potency compared to non-conjugated antisense drugs. Triantennary N-acetyl galactosamine (GalNAc, GN3), a subset of LICA technology, is designed to enhance the delivery of antisense oligonucleotides (ASOs) to hepatocytes. LICA technology can target additional cell types by means of different ligands.

Technology: Denali Transport Vehicle (TV) Platform
Most Advanced Stage: Phase 2
Technology Category: Brain Targeting; Receptor Carrier
Company: Denali Therapeutics/F-Star Biotechnology
Notable Pipeline: Phase 2 - DNL310 (Hunter Syndrome), DNL343 (ALS)
Notable: The TV platform encompasses four related platforms directed to the delivery of antibodies (ATV), enzymes (ETV), oligonucleotides (OTV), and proteins (PTV) to the brain.
Technology Summary: This technology is based on (TfR)-specific Fcab (antibodies), Fc-enzyme fusion (enyzmes), Fc-oligonucleotide fusion (oligonucleotides), or Fc-protein fusion (proteins) constructs, which engage transferrin receptor (TfR) on the blood vessel wall in the brain. The engineered TfR bound molecule is delivered into the brain via receptor-mediated endocytosis. Antibodies engineered with the ATV technology have demonstrated a 20-fold greater brain penetration than control antibodies. ATV platform technology also utilizes the blood brain barrier receptor binding Fc domain to engineer bispecific and bivalent antibodies.

Technology: MedRing
Most Advanced Stage: Phase 2
Technology Category: Vaginal Inserts/Devices; Drug Delivery Compliances
Company: LiGalli
Notable Pipeline: Phase 2 - LIG MR1 (Therapeutic, Overactive Bladder), LIG MR16 (Diagnostic, Compliance)
Notable: Unique 'intelligent' vaginal ring delivery system with pump, liquid drug reservoir, and supporting electronics to permit connected therapeutic and diagnostic applications
Technology Summary: MedRing comprises a flexible ring-shaped device that can be manually collapsed and which assumes an extended shape when little to no external force is being applied. It can be inserted and removed by the patient, assuming a position in the posterior fornix of the vagina. MedRing contains a miniaturized liquid formulation drug container with pump, battery, antenna, electronics, and sensors. Current prototypes include sensors to monitor temperature and confirm drug delivery. It can also be equipped with sensors that monitor other kinds of biometric data, such as glucose levels and ovulation status. MedRing can be controlled for adjustment of dose, schedule, and timing with a smart phone. Drug compounds with a low bioavailability or high first-pass effect are well suited.

Technology: Q-Sphera
Most Advanced Stage: Phase 1
Technology Category: Biodegradable PLGA Microspheres; 3D Printing
Company: Midatech Pharma
Notable Pipeline: Preclinical - MTD-211 (CNS), MTD219 (anti-rejection), MTX-214/MTX216 (undisclosed)
Notable: The use of 3D printing technology to encapsulate biological drugs into PLGA based microspheres providing sustained release injectable depot formulations for up to 6 months
Technology Summary: The bioencapsulation process involves two or more fluid phases containing a polymer and the biological material. These are pumped continuously into a microfluidic device in which they are segmented into discrete droplets with an immiscible liquid phase. Droplets are cured into solid beads using benign chemical, UV, or phase change methods. Monodisperse particles can be manufactured in the size range of 25-2000 microns. Working with model antibodies, Midatech has demonstrated encapsulation and preservation of functional integrity and antigen binding in vitro. The Q-Sphera platform does not use surfactants, toxic solvents, biphasic mixtures, shear, or heat forces and permit use with a wide range of solvents, bioresorbable polymers, and stabilizing excipients to finely tune product characteristics. product characteristics.

ARTIFICIAL INTELLIGENCE

Modernizing Your Clinical Development Safety Practices With Artificial Intelligence

By: Updesh Dosanjh, MS

INTRODUCTION

Digital transformation has been shaking up the pharmaceutical industry for the past decade as the value of technology becomes apparent, but also increasingly necessary for business continuity in the face of rapidly growing health data.[1] In fact, artificial intelligence (AI) is believed to be the most disruptive technology to the pharmaceutical industry in 2021.[2]

Though still relatively nascent in parts of the pharmaceutical industry, AI and machine learning (ML) have already been explored for numerous use cases across the continuum of drug development, delivery, and post-market activities with some success. Among these, leveraging AI/ML for safety processes in clinical research as well as post-market pharmacovigilance (PV) hold tremendous value for organizations to process and extract more insight from clinical trials preemptively, improving the safety of new products for patients.

AI IN POST-MARKET PHARMACOVIGILANCE

AI/ML as well as natural language processing (NLP) have an inherent value to post-market pharmacovigilance. In a post-market environment, pharmaceutical companies are in a position of knowing a lot about their product but not a lot about the individual patients receiving it. Once a product is on the market, the patient population receiving it is infinitely larger than in a clinical trial setting, and data about them and their reported experiences is increasingly disparate. For instance, they may switch doctors, which can fragment their medical history. Additionally, they could be reporting their experiences to their doctors, to a call center, or even on forums and social media. Nevertheless, it's the responsibility of the pharmaceutical company to capture and create as holistic of a picture as possible to identify potential adverse events. At the rate data is both growing in volume and becoming more disparate, this is simply not a problem that companies can hire their way out of.

NLP supports post-market pharmacovigilance by converting information from text-based sources, such as doctor's notes in electronic health records, call center transcriptions, and social media, to a structured format that can be read by a computer. From there, AI/ML can fulfill its most essential purpose: analyzing massive amounts of captured health data to identify significant data points. For safety teams, applying AI/ML helps them to spot potential adverse events to review and subsequently supports the automation of reporting.

BRINGING AI TO THE CLINICAL RESEARCH PROCESS

The value of AI/ML for safety in clinical development may be less inherently obvious to pharmaceutical companies exploring use cases compared to a post-market environment. Due to the necessarily stringent requirements for qualified patients in randomized clinical trials (RCTs), there are a very small number of patient cases to observe. What's more, in a clinical research setting, medical professionals have the luxury of knowing a lot about the drug in question as well as the individual patients. However,

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every case in an RCT is disproportionately more important than in a real world, post-market setting. Researchers have an imperative to uncover every possible safety outcome in clinical development to streamline the approval process and mitigate safety challenges when the drug is approved and available to patients.

Simply put, the use of these technologies in clinical research is fundamentally the same as in post-market activities. The key difference is a focus on analyzing depth of patient information versus breadth, looking at one case at a time. Reducing the opportunity for human error in data capture and analysis will help researchers to identify potential safety concerns more holistically and deliver safer treatments to patients, making the jobs of safety teams easier in the more reactionary post-market environment.

CLINICAL RESEARCH USE CASES THAT BENEFIT FROM AI FOR SAFETY

Applying AI/ML to clinical trial data analysis will have a tremendous amount of value for virtually any type of clinical trial. Any tool that aids in making sense of data and uncovering all possible outcomes will be beneficial to the creation of safe, holistically researched treatments as well as contribute to faster timelines and lower R&D costs by mitigating manual analysis. However, there are key emerging use cases that stand to see significant value from the use of these technologies.

Remote & Hybrid Trials

Following the pandemic, remote and hybrid RCTs are primed to become the new standard for trials. Some things, such as blood work and physical examination, will always require in-person visits, but the realized capability to glean data remotely offers contract research organizations the opportunity to expand their recruitment efforts and better retain patients for the duration of the RCT.

Strategies for ensuring the quality of data from remote trials is on par with what regulators have come to expect from traditional trials are currently being explored. By their nature, remote RCTs primarily glean patient-reported outcomes. Furthermore, measures must be taken to fill in gaps in the absence of physically seeing the patient. For example, if patients are asked for their pain level on a scale of 1 to 10, this might be more easily gleaned in person while a patient report could vary significantly by individual. As this trial format becomes more and more ubiquitous, AI and NLP capabilities help structure this information and notice trends that can contextualize findings for deeper understanding and accurate conclusions.

Longer Clinical Trials

Similar to the post-market environment, patient and drug information is often available to clinical researchers in text-based formats, such as patient ques-

tionnaires. This necessitates the use of NLP tools to analyze and process that information. This capability can be particularly valuable in longer RCTs, during which researchers must analyze patient histories and drug results over an extended period of time. Many RCTs have long document trails and questionnaires that can add up to hundreds of pages of patient data that researchers must analyze.

High Risk Drug Trials

The ultimate goal of an RCT is to determine if the benefits of a drug outweigh its risk so that it can go to market and help patients. To this end, AI is especially valuable in higher risk drugs, in which a researcher may know that a treatment cures or alleviates an illness or condition but comes with the potential for unpleasant side effects. NLP and AI can be applied to datasets to produce word clouds of potential signals that patients would be more likely to experience negative side effects. This can be valuable in helping researchers notice safety trends and issues they were not looking for to begin with.

REGULATORY & INDUSTRY ADOPTION OF AI IN CLINICAL TRIALS

As the technology matures and its use cases for the industry expand, AI capabilities have shifted from a buzzword add-on to treatment development and delivery processes to a foundational tool for success. Leaders in the pharmaceutical industry have long been viewed of skeptics of digital transformation. However, the challenges they are increasingly faced with in research as well as post-market to process data in near real time are ones they cannot solve with more hiring. These hurdles have been the catalyst for a change in tune that can be seen not just across the industry, but with regulatory bodies as well.

The industry will surely benefit from the adoption of AI-driven safety practices. In the highly regulated pharmaceutical industry, leaders must feel confident the AI they implement can intuitively adapt to data privacy rules, regulatory reporting requirements, and ultimately glean the insight necessary to validate the safety of products.

Regulators are similarly exploring the ways in which AI can be implemented reliably for clinical development. Regulations around how AI can be used is forthcoming from the Food and Drug Administration (FDA) and others. In the meantime, regulators are certainly encouraging companies to implement AI to aid in the exploration of its value. They recognize that anything that cuts the cost of clinical trials opens up more opportunities for more innovative drugs, especially those for smaller and more rare groups of people, are a good thing.

SUMMARY

A higher level of analytics is required to succeed in the face of evolving challenges in life sciences. Advancing our understanding of human health through better, more insightful decisions will promote a new era of innovation in drug development as we simultaneously explore new classes of medicines like mRNA and precision treatments as well as new research methodologies like remote trials. The proven promise and potential of AI and ML to accelerate drug discovery while cutting costs and risks will be the underpinning for ushering in this new era. The insights these technologies enable researchers to uncover will go beyond routine processes to support the discovery of new product indications. By continuing to explore the ability of these technologies to deliver better and safer treatments, pharmaceutical companies can benefit not only the advancement of the medical community, but the quality of life of patients around the world. ◆

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BIOGRAPHY

Updesh Dosanjh, as Practice Leader for the Pharmacovigilance Technology Solutions business unit of IQVIA, is responsible developing the overarching strategy regarding AI and Machine Learning as it relates to safety and pharmacovigilance. He has more than 25 years of knowledge and experience in the management, development, implementation, and operation of processes and systems within the life sciences and other industries. Most recently, he was with Foresight and joined IQVIA as a result of an acquisition. He earned his Bachelor's degree in Materials Science from Manchester University and his Master's degree in Advanced Manufacturing Systems and Technology from Liverpool University.

Drug Development
EXECUTIVE

Tom Sellig

CEO

Adare Pharma Solutions

Adare Pharma Solutions: The Journey to Become a Full-Service Provider

Tom Sellig was excited to take over the role of CEO at Adare Pharma Solutions in January because he saw a unique chance to make a difference, create value, and seek out growth opportunities. He and the leadership team at Adare are confident that the company is now well positioned on its journey to become a world-class, full-service CDMO, thanks to the company's expanded development and manufacturing capabilities, its growing biome-based business, and the Frontida BioPharm acquisition this past December.

Mr. Sellig recently spoke with *Drug Development & Delivery* about his expectations for Adare and how he can leverage his 30-plus years of pharma experience to put Adare in a competitive position to address complex formulation and development challenges. He also addressed how acquiring Frontida, a vertically integrated CDMO focused on oral formulations, will help build and expand Adare's customer relationships.

Q: What mark are you hoping to make as the new CEO of Adare?

A: There are certain segments within our business, offering more opportunity than we realized, and other areas that we are less excited about. You learn to minimize certain areas of the business and maximize other larger growth opportunities. Specifically, I am referring to our technologies and our biome business, the latter residing in a space that is exploding and for which we are well positioned. We are also focused on how we go to market with our customers, our messaging, and taking advantage of the technology, assets, and capabilities that we have not really gone

after in the past. The legacy Adare business offers taste masking, controlled release, and patient-centric dosage forms. When combined with Frontida's capabilities of high potency, comprehensive packaging, and multi-layer tableting, we now can offer a suite of technology services to help customers develop products and address their formulation challenges. Combined, the company now has nearly 100 scientists and experts in product development to create customized solutions for customers worldwide.

Q: Please describe Adare's biome business.

A: Adare Biome™ is our specialized division located in Houdan, France, near Paris, where our team is focused on harnessing the power of the microbiome. Biotic-based products are growing at a significantly faster rate than the rest of the market. We see leading pharma companies, and even growing mid-sized companies, focused on biome-based solutions. Using our proprietary LB (*Lactobacillus fermentum and Lactobacillus delbrueckii*) strains and the ECHO™ Process to enrich, concentrate, and heat treat organisms, Adare Biome provides post-biotic solutions in human and animal health. Our own Lactéol® is a proprietary combination of LB and fermented culture medium (neutralized and enriched with metabolites) that safely fights diarrhea, in addition to rehydration and/or dietary measures, in children and adults, using a unique combination of actions to inhibit pathogens and boost natural defenses. We see this biome business as a growth opportunity for our organization and we plan to make additional investments to scale this business.

Q: As you joined Adare right after the Frontida acquisition, do you have your own vision now for how the two companies move forward?

A: Our investors believed there were opportunities that existed between the two organizations. And I am aligned with most of that rationale, as well as the strategic and financial drivers. When it comes to taking those messages and capabilities to customers, we see additional upside opportunities. We are committed to helping our business development teams and customer management teams converse with customers. I have significant experience driving growth and thinking about scaling customer solutions to be more specific around our solutions and benefits to customers, such as integrated solutions that can mean faster development cycles, creative cost reduction strategies, and overcoming formulation challenges.

Q: How does the Frontida acquisition expand Adare's capabilities, capacity, and expertise and how will you brand this message to pharma clients?

A: The overall response is capacity and scale. We have added three new sites into our overall network, two in Philadelphia and one outside Chicago in Aurora, IL. We have added tremendous development and commercial manufacturing capacity. Additionally, we brought in experts who have both complementary and differing skill sets from our existing Adare team. Finally, we now offer capabilities in high potency, multi-layer tableting, and packaging. The synergy between the two companies gives us full-service capabilities without needing to use third-party providers to provide end-to-end solutions for our customers. Most clients in the industry have worked with either Adare or Frontida in the past. They know Adare as a product-based organization, but now they will know us as a service-based organization.

Q: What is Adare's business model and does the acquisition change that model?

A: At our core, we are a technology-driven CDMO that has end-to-end capabilities, from early-stage development through commercial manufacturing, including packaging capabilities and capacity. We will continue to add capabilities to fill gaps and double down on the breadth of capabilities and capacity we bring to the market. We will expand customer relationships and geographical footprint to build out the vision of developing products and addressing formulation challenges.

Q: How will Adare position itself against other CDMOs going forward?

A: This goes back to our core technology-driven platform and leveraging our broad-based solutions. As I think about the CDMO space today, there are players looking to provide solutions for cell and gene therapy, biologics, and sterile. Then there are some international CDMOs focused on cost. I think

about differentiation through service and technology. These are the areas where we can build a world-class leading CDMO that specializes in small molecule and oral delivery solutions. About 90% of the volume in global pharma is in small molecule. While other segments may be growing, this continues to be an important space. Being able to support those products and looking for better solutions for generics or new NDAs is where we want to create our position in the market.

Q: Are there specific therapeutic areas that interest Adare?

A: We actually went through a formal, comprehensive analysis of the global drug development pipeline and looked at every product in clinicaltrials.gov. We identified where they are in their development cycles and matched that with our capabilities, both in development and commercial manufacturing. What we found was that we are able to cover most therapeutic areas. Some don't fit into our sweet spot, but we can support quite a wide range of products that cover virtually all the therapeutic areas.

Q: What keeps you up at night?

A: The things I don't worry about are our quality, regulatory compliance, operational performance, and delivery – all of which are very strong. I do worry about how to bring our solutions to more customers, how to scale, and how to keep up with the latest technological needs in the industry. I think about the numerous things on our roadmap to become a world-class CDMO and feel confident that we are well on our way. ◆

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FREEZE-DRYING MICROSCOPY

Unravelling the Complexities of Freeze-Drying Pharmaceuticals With Advanced Microscopy Techniques

By: Paul Matejtschuk, PhD, Prof Yvonne Perrie, and Duncan Stacey, PhD

INTRODUCTION

Degradation of stored material, either through autolysis or the growth of spoilage organisms, is primarily dependent on the presence of water. Products that are prone to degradation, such as food and pharmaceuticals, must be stabilized by immobilizing or reducing of the water content. For example, vaccines and other biological materials can be stabilized by chilling or freezing, but transporting samples in a frozen state is expensive, and breakdown of freezers may result in the complete loss of valuable product. Alternatively, water can be removed from labile products through air-drying using high processing temperatures, but this can alter the product's physical and chemical properties and is therefore unsuitable for pharmaceuticals.[1]

Freeze-drying (lyophilization) removes most of the water in a sample under low temperature and vacuum conditions, providing a dry, active, shelf-stable, and readily soluble product. It is therefore a widely used technique in the manufacture of protein biomolecules for therapeutic and diagnostic applications.[2] As well as stabilizing drug products for transport and preventing degradation, freeze-drying reduces the volume of the sample, thus it requires less storage space and can be stored under ambient conditions.

Lyophilized drugs are representing an increasing proportion of the market, with the upward trend particularly strong in the biologics segment, where innovation and drug development is advancing rapidly. In addition, the complexity and strict storage conditions needed to preserve the biological drug activity make freeze-drying a popular formulation technique.

Although used by laboratories since the 1880s and upscaled to industrial scale in the 1930s with commercially available systems, freeze-drying is an incredibly complex process, and research is ongoing to better understand and optimize the process. The three main stages of the freeze-drying cycle (freezing, primary drying, and secondary drying) are often altered and adapted to specific properties of a drug product, and adjustments may be required when scaling up from research and development (R&D) to production. In addition, freeze-drying is a notoriously lengthy process, so pharma and biotech companies can decrease costs by optimizing freeze-drying protocols to speed up timelines and increase product yields.

DIGGING DEEPER INTO LYOPHILIZATION

Being able to directly visualise the freeze-drying process is essential in minimizing the time and cost it takes to develop a protocol for drug development and manufacture. Freeze-drying microscopy (FDM), first developed in the 1960s, combines light microscopy techniques, such as phase contrast and polarized light, with a thermal stage that can accurately control temperature and pressure.

FDM has since become a widely used method that can uniquely determine how a drug product will react to different

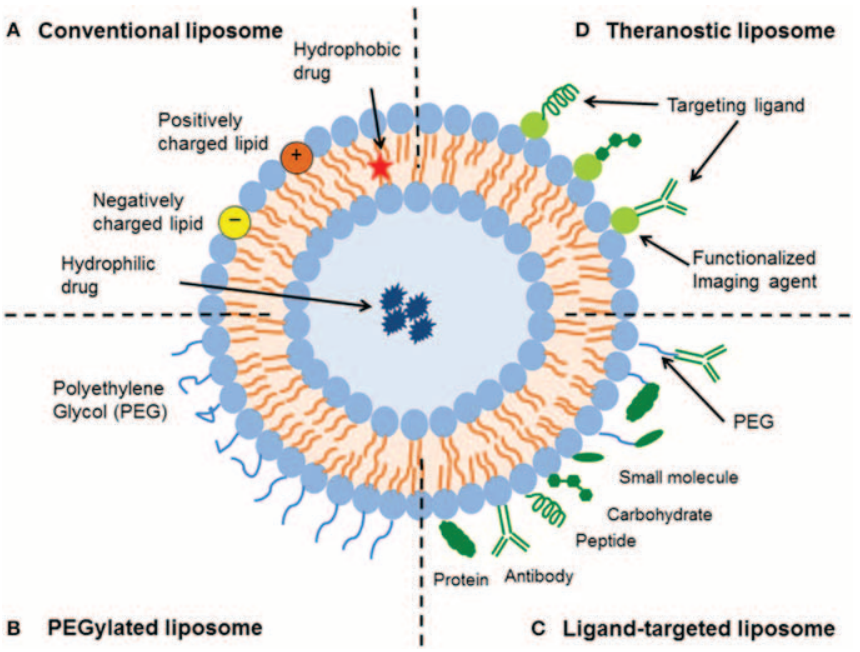
thermal conditions. Of particular interest are the temperature and pressure required for each of the freezing and drying stages. One of the critical parameters is the collapse temperature (Tc) – the temperature at which the structure of the formulated product weakens and is no longer able to support itself – which can only be reliably measured using FDM. FDM can also be used to determine the eutectic temperature (Teu) – the lowest possible melting temperature over all of the mixing ratios for the involved component species in a mixture of substances – and the potential formation of a barrier due to formation of a product/matrix "skin."

Researchers at the UK's National Institute for Biological Standards and Control (NIBSC), led by Dr Paul Matejtschuk, are using the latest FDM technology to investigate the development of formulation and freeze-drying processes, with a focus on protein therapeutics. The group uses FDM to establish how different formulations affect the freeze-drying process; for example, how drug manufacturers can overcome the challenges of freeze-drying from organic solvents, or stabilizing drug delivery systems such as liposomes.

OPTIMIZING FREEZE-DRIED LIPOSOMAL FORMULATIONS

Liposomal delivery systems are increasingly used in the pharmaceutical industry due to their versatility and their unique ability to entrap both lipophilic and hydrophilic compounds. There are four main types of liposomal delivery platforms that offer varying degrees of stability and specificity (Figure 1).

FIGURE 1



Schematic representation of the different types of liposomal drug delivery systems. (A) Conventional liposome – Liposomes consist of a lipid bilayer that can be composed of cationic, anionic, or neutral (phospho)lipids and cholesterol, which encloses an aqueous core. Both the lipid bilayer and the aqueous space can incorporate hydrophobic or hydrophilic compounds, respectively. **(B)** PEGylated liposome – Liposome characteristics and behavior *in vivo* can be modified by addition of a hydrophilic polymer coating, polyethylene glycol (PEG), to the liposome surface to confer steric stabilization. **(C)** Ligand-targeted liposome – Liposomes can be used for specific targeting by attaching ligands (eg, antibodies, peptides, and carbohydrates) to its surface or to the terminal end of the attached PEG chains. **(D)** Theranostic liposome – A single system consisting of a nanoparticle, a targeting element, an imaging component, and a therapeutic component. [Reproduced from reference 3 in accordance with Creative Commons Attribution License (CC BY)]

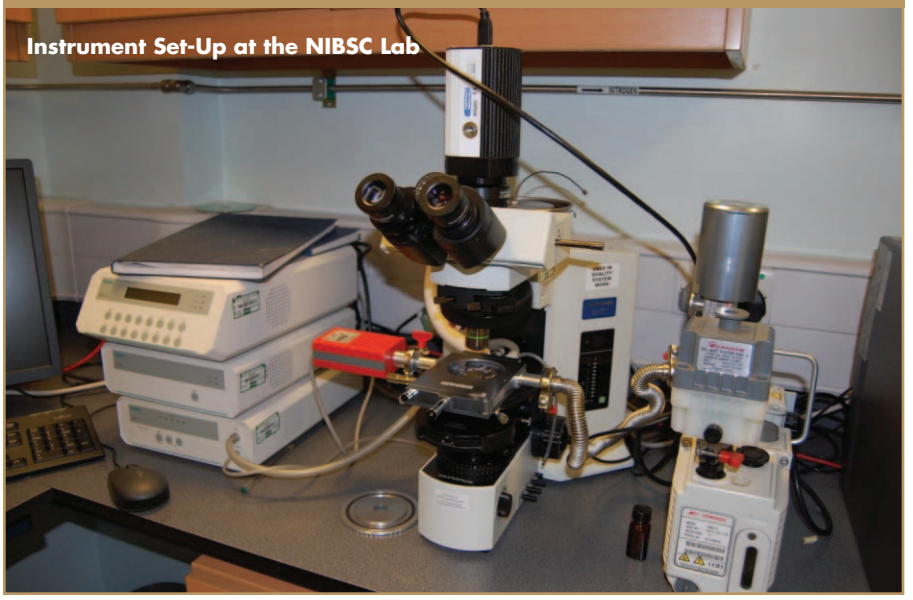
Although there are many liposomal drug formulations currently in clinical trials and several on the market, their high cost and challenges surrounding physical and chemical stability have limited their widespread commercial development.

Liposomes are prone to oxidation or hydrolysis caused by chemical and physical degradation, drug leakage, formation of aggregates, and fusion.[4,5] These changes can alter a drug's formulation properties, affecting not only the product's shelf-life, but also the *in-vivo* bio-distribution and pharmacokinetic properties of the drug formulation.[6-8]

Although aqueous liposomal formations are available on the market, their susceptibility to chemical and physical degradation, as well as the cost of cold-chain distribution, mean that other methods of stabilization are often required. Freeze-drying is therefore a popular and widely studied technique for stabilizing liposomal delivery systems.

The team at NIBSC and Strathclyde recently investigated the liposomal freeze-drying process to improve its reproducibility and compatibility with the high-throughput screening of liposomes. Specifically, the study aimed to identify the formulation and process parameters ideal for the freeze-drying of empty and protein loaded liposomes using Ovalbumin (OVA).[9] The group also considered the formulation parameters with regard to presence of protein, lipid selection, lipid

FIGURE 2



charge (neutral, cationic, and anionic), lipid concentration, and the final concentration of the cryoprotectant sucrose, as all of these factors are known to influence freeze-drying. Formulations were freeze-dried in both 96 well plates and vials in parallel.

FDM was used to predict the ideal freeze-drying conditions for liposome-cryoprotectant mixtures, by enabling an estimation of the freezing, collapse, and melt temperatures using a cryostage (FDCS196, Linkam Scientific Instruments) mounted on an optical microscope (BX51, Olympus) connected to a control unit and Liquid Nitrogen Pump (T94 and LNP, Linkam Scientific Instruments).

The samples were frozen using liquid nitrogen at a rate of 10°C/ min until -50°C was reached, after which the temperature was held for 2 minutes before drying was started by applying a 0.1mBar vacuum. To establish the collapse and melt of the samples, the temperature was then ramped up to 20°C at a controlled rate. Images were taken every 20 seconds for the duration of the cycle and physical changes to the liposomal formulations could be observed in real-time (Figure 3).

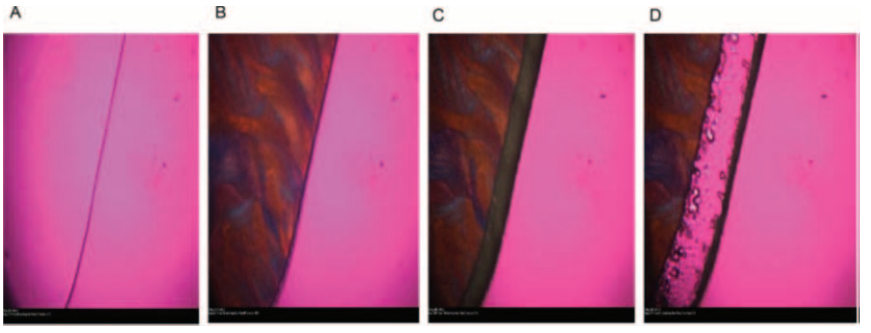
Results showed the presence of protein adds stability to both neutral and charged formulations, with the same amount of OVA retained after freeze drying (Table 1). The minimal to no leakage of the OVA suggests that pre-cooling the shelf and rapid freezing could prevent egress resulting from the formation of large crystals. In contrast, the liposomal size changed upon rehydration, with cationic liposomes showing the greatest increase in size.

The study demonstrated the ability to freeze-dry liposomal formulations in microplates, as well as vials for the rapid screening, preservation, and optimization of liposomal formulations. Liposomal physicochemical characteristics were preserved regardless of the formulation type, with no loss of protein observed. This positions the freeze-drying process outlined in this experiment as a feasible, transferable, quantifiable, and rapid method for screening and improving the longevity potential of pharmaceutical liposomal products.

OPTIMIZING TOMORROW'S DRUGS

As the biologics market continues to grow, the demand for lyophilized formulations is set to increase. Biopharma companies, when scaling up freeze-drying processes from the development stage, require methods to examine each stage and optimize the speed and cost of

FIGURE 3



Freeze drying microscopy of OVA- containing 1mg/ml 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC):Chol liposomes, formulated with 7.5% sucrose. Magnification was 20x using plane polarized light. A two microlitre aliquot was frozen at a rate of 10°C/min to -50°C (image A), with the freezing point of this sample occurring at -18.6°C (Image B). Drying was achieved by application of a 0.1mBar vacuum and the temperature then being raised at a controlled rate. Drying was observed below the collapse temperature (Image C), which was determined to occur around -34°C (Image D). (Reproduced with permission from International Journal of Pharmaceutics)[9]

TABLE 1

Formulations	Lipid Concentration (mg / mL)	Ovalbumin (mg / mL)	Sucrose (%)	EE Before (%)	EE After (%)
DMPC:Chol	4	0.25	5	37 ± 0.2	36 ± 0.2
	4	0.25	10	37 ± 0.2	37 ± 0.3
	10	0.25	5	39 ± 0.3	33 ± 1.0
	10	0.25	10	39 ± 0.3	40 ± 3.0
DSPC:Chol	4	0.25	5	34 ± 0.3	30 ± 0.7
	4	0.25	10	34 ± 0.3	33 ± 0.2
	10	0.25	5	36 ± 0.5	35 ± 1.1
	10	0.25	10	36 ± 0.5	34 ± 0.4

Characterising empty and Ovalbumin (OVA) encapsulation efficiency (EE) (as a % of 0.25 mg/mL initial OVA) 1,2-dimyristoyl-sn-glycero-3-phosphocholine (DMPC):Chol and 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC):Chol liposomes post freeze-drying. A range of formulation variables, including lipid concentration, type, and amount of final sucrose concentration, was investigated. The physicochemical properties (size and polydispersity) were measured using dynamic light scattering, with encapsulation calculated using high-performance liquid chromatography coupled with evaporative light scattering detector (HPLC-ELSD). The results represent three batches, ± SD.(Reproduced with permission from International Journal of Pharmaceutics)[9]

the process. The availability of accurate FDM methods is therefore vital for the in-depth investigation of freeze-drying processes and structures. Freeze-drying proteins presents unique challenges due to the need to preserve their biological activity, necessitating equipment that can measure parameters, such as Tc and Te, to ensure the correct temperatures are adhered to.

FDM is being used to analyze the most challenging formulations, such as liposome drug delivery systems, that require sophisticated stabilization methods. By altering and adapting the three main freeze-drying stages to specific formulations, researchers at NIBSC are providing the tools needed for the pharma industry to improve its drug development processes and maintain drug stability when scaling up to production. ◆

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BIOGRAPHIES

Dr. Paul Matejtschuk leads a team in the development of formulation and freeze- drying processes for the WHO International Standards and other reference materials produced by NIBSC, a centre of the Medicines & Healthcare products Regulatory Agency. He has over 30 years post-doctoral experience across downstream processing, including lyophilization. His most recent focus has been in the biological application of thermal analysis, formulation, and lyophilization of biologicals, high throughput screening methods, application of Design of Experiments (DoE) and Process Analytical Technology (PAT) in freeze-drying as well as the measurement of residual water and its impact on the stability of biologics.

Prof. Yvonne Perrie is Professor in Drug Delivery within the Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, Glasgow, Scotland. Her research is multi-disciplinary and is focused on the development of drug delivery systems to facilitate the delivery of drugs and vaccines, thus providing practical solutions for current healthcare problems. She is an internationally recognized expert in the field of liposomes and particulate drug delivery research with a strong track-record of high impact publications, with approximately 130 peer-reviewed manuscripts plus 5 textbooks and 6 patents.

Dr. Duncan Stacey is Sales and Marketing Director at Linkam Scientific Instruments. He is focused on the development of new markets and strategic OEM partners and he brings a wealth of technical and commercial experience to Linkam. Before joining Linkam, he worked in Sales, Marketing, and Product Development for some of the leading photonics companies in imaging, spectroscopy, and microscopy. He earned his PhD in 1993 from University of Liverpool in Optics and Spectroscopy.

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SODIUM STEARYL FUMARATE **(Core/Content)**	29.29 mg
COLLOIDAL SILICON DIOXIDE **(Core/Content)**	7.58 mg
POLYVINYL ALCOHOL, UNSPECIFIED **(Tablet/Capsule coat)**	11.72 mg
POLYETHYLENE GLYCOL **(Tablet/Capsule coat)**	5.92 mg
TALC **(Tablet/Capsule coat)**	4.33 mg
FERRIC OXIDE YELLOW **(Tablet/Capsule coat)**	0.32 mg
TITANIUM DIOXIDE **(Tablet/Capsule coat)**	7 mg
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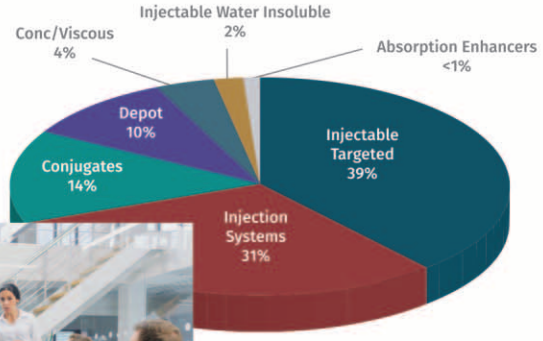

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Special Feature

PFS & Parenteral Drug Delivery: Self-Injection is Very Much the "New Normal"

By: Cindy H. Dubin, Contributor

Covid-19 fast tracked the healthcare industry's growing acceptance of patient self-injection, enabling patients to continue treatment outside of hospital environments and within outpatient facilities and home-care settings. And prefilled syringes (PFS) represent the fastest-growing self-injection segment. In 2021, the global prefilled syringes market was valued at $5.8 billion. Overall, the market is expected to grow to $12.7 billion by 2028.[1]

"Self-administration of injectable drug products via pen injector, autoinjector or prefilled syringe has been a growing market trend predating the occurrence of the COVID-19 pandemic," says Eric Lee, Business Development Director, Novocol. "Following COVID, it is anticipated that self-administered injectables will continue to rise as a result of the development of novel therapeutics, biosimilars, and differentiation of existing marketed injectable products. This trend will lead to improved patient convenience while reducing the burden on healthcare systems and practitioners."

Ziv Cahani, Vice President Business Development and Marketing at DALI Medical, agrees. The industry is well-positioned to keep pace, as there is a growing variety of solutions already available for injectable drug delivery in home settings, and many more in development. These include safety needles and safety syringes, connected injectable delivery devices, and advanced platforms for managing and analyzing compliance. Additionally, device manufacturers are developing unique solutions specifically designed for self-injection – which is very much the "new normal."

Oval Medical's ArQ-Bios platform is for subcutaneous delivery.

As COVID continues to impact the research and development focus across the globe and the desire to achieve a new normal, August Bioservices expects innovators to invest further in therapies that take advantage of the ready-to-use format. "We know from decades of experience that there has long been a preference for ready-to-use" products, as they are more user-friendly, can help to save time and can help to reduce the risk of medication errors," says Ryan Downey, Director of Customer Operations, Commercial Development, August Bioservices.

As an example, BD Medical - Pharmaceutical Systems is investing $1.2 billion over a 4-year period to expand and upgrade manufacturing capacity and technology for PFS and advanced drug delivery systems across its six global manufacturing locations, and will add a new manufacturing facility in Spain. The investment is also funding capacity expansion, new product innovations, manufacturing technology enhancements, and business continuity improvements across the existing BD network. "These initiatives are all designed to maximize supply and reduce risk for pharmaceutical companies that rely on ready-to-fill syringes for their injectable drugs – including complex biologics, vaccines, and small molecules," says Marie-Liesse Le Corfec, Head of Global Portfolio Marketing, BD Medical - Pharmaceutical Systems.

This exclusive *Drug Development & Delivery* annual report showcases how leading CDMOs and drug delivery developers are responding to this and other market trends to create ergonomic technologies that are patient friendly, easy to use, reduce needle anxiety, and feature improved packaging materials.

Ajinomoto Bio-Pharma Services: Multi-Purpose Filling is Flexible & Quick

With six automated aseptic filling lines, Ajinomoto Bio-Pharma fills clinical and commercial drug products into vials, syringes or cartridges. But before a client's drug product makes its way to the filling line, there is a tremendous amount of work, focus, and preparation for the aseptic fill. "The operations team cleans, validates, prepares, and plans for the formulation, sterile filtration, and fill of life-saving products," says Roland Kim, Manager, Drug Product Manufacturing, Ajinomoto Bio-Pharma Services. "In addition, the quality team inspects and tests the aseptic environment in preparation for the fill."

Aji Bio-Pharma has invested and expanded services with the addition of a multi-purpose filling line for clients needing a quick timeline for scheduling, as well as flexibility in the config-

Aji Bio-Pharma's high-speed, flexible filling line at its San Diego facility.

uration with the option to fill into vials, syringes or cartridges, expains Mr. Kim. "In addition, we are continuing to offer virtual solutions to help our clients across the globe that may still have travel restrictions or difficulties. These include remote suite viewing, secure document sharing, and remote audits."

Another difficulty Aji Bio-Pharma has witnessed revolves around supply chain issues, especially with sourcing components. Mr. Kim describes how a large syringe client contacted Ajinomoto Bio-Pharma Services regarding a project with components and fill volumes out of normal operating ranges. "Our drug product subject matter experts were presented with a challenge to order new change parts, create a new fill curve, and validate the process within a timeline that would meet the client's needs," he says. "A cross-functional approach was taken to produce a robust and repeatable process for the client's campaign. Being able to fill syringes that are lighter material and have a wider OVS tip versus the barrel's outer diameter, and 50% less fill volume, was a success for Aji Bio-Pharma in helping our client achieve its goal."

ApiJect Systems, Corp.: Continues to Develop Flexible BFS-Based Injection Platform

ApiJect works with pharmaceutical and biotech companies to fill/finish their injectable drug products into single-dose, prefilled injectors in a highly efficient and scalable way. This is achieved by first designing a Blow-Fill-Seal (BFS) Container that is customized to the specific drug product. Then, a prototype BFS-based prefilled injector is manufactured, tested for performance, and rapidly iterated until the pharma company is satisfied with the results, explains Josh Myers, Senior Director, Supply Chain, ApiJect Systems, Corp. Finally, the ApiJect team helps the pharma company either set up the necessary BFS manufacturing line in their facility or connect them with a contract manufacturer that has the necessary BFS experience and equipment.

ApiJect primarily addresses three major challenges in the US and global injectables fill/finish market.

1) Scalability with Efficiency: "Prefilled syringes can be time-consuming to fill/finish and costly to manufacture compared to traditional vials and disposable syringes," says Mr. Myers. "A high-capacity BFS production line fill/finishes up to 25 prefilled single doses every 3-7 seconds."

2) Flexibility: Traditional parenterals packaging is often confined to existing container sizes and shapes, which can only be manufactured and filled/finished by dedicated plants and equipment that can take years to establish, explains Mr. Myers. "BFS machines leverage molds that can be custom designed and rapidly changed out to produce a variety of shapes and sizes to meet requirements of a broad range of sterile liquids."

3) Compact Supply Chain: BFS-based injectors made on the ApiJect Platform have two primary raw materials (stainless steel for needles, pharmaceutical-grade plastic resin for containers and attachable components). "And the entire fill/finish process, including the primary container manufacturing, can be done under one roof," explains Mr. Myers. "This short, resilient supply chain enables onshoring and reliable production."

As of this time, any device made on the ApiJect Platform has not been cleared by the FDA or other regulatory body. However, the scale, compact supply chain, and flexibility of the ApiJect Platform were outlined in a coordinated project with the US Department of Defense and Department of Health and Human Services in 2020 as part of America's initial response to COVID-19, descrbes Mr. Myers. "ApiJect and related partners were able to upgrade three existing BFS lines at The Ritedose Corporation within 7 months to be capable of filling and finishing up to 45 million prefilled injectors a month with potential COVID-19 vaccine."

He adds that while this capacity has not been utilized to date thanks to the success of more traditional domestic fill/finish supply chains, it proved the scale and efficiency enabled by the ApiJect platform, which has led to increased coordination with pharmaceutical, biotech, and contract manufacturing companies. This includes a recently announced project with Fareva to establish three similar-capacity BFS lines at one of its facilities in France for vaccine fill/finish.

Aptar Pharma: Derisking the Development of Prefilled Syringe Delivery

Primary packaging plays a critical role in the development and delivery of every injectable drug and offers many opportunities to meet evolving market expectations. Thus, primary packaging manufacturers have been improving their processes and are working with material sciences to develop innovative solutions, such as rubber components laminated with fluorinated films (i.e. ETFE). "While Halobutyl formulations are specifically designed to limit their chemical interaction with therapeutics, ETFE films form an additional barrier that further reduces the transfer of extractables and leachables into the drug product," says Claire Raynal-Olive, Vice President of Business Development for Aptar Pharma. "Coated components help drug developers meet the stringent requirements of regulatory agencies and reach the market faster."

Additionally, as the demand for self-injection increases, primary packaging manufacturers must also guarantee that the functional performance of their components (such as the activation and gliding forces) is congruent with patients' capabilities or autoinjector integration. "Such functional requirements are further emphasized as drug developers work toward reducing the frequency of injection for improving patient compliance and comfort," she says. "Functionality issues can be avoided by selecting premium components designed to deliver consistent performance, whether for manual injection or autoinjector integration."

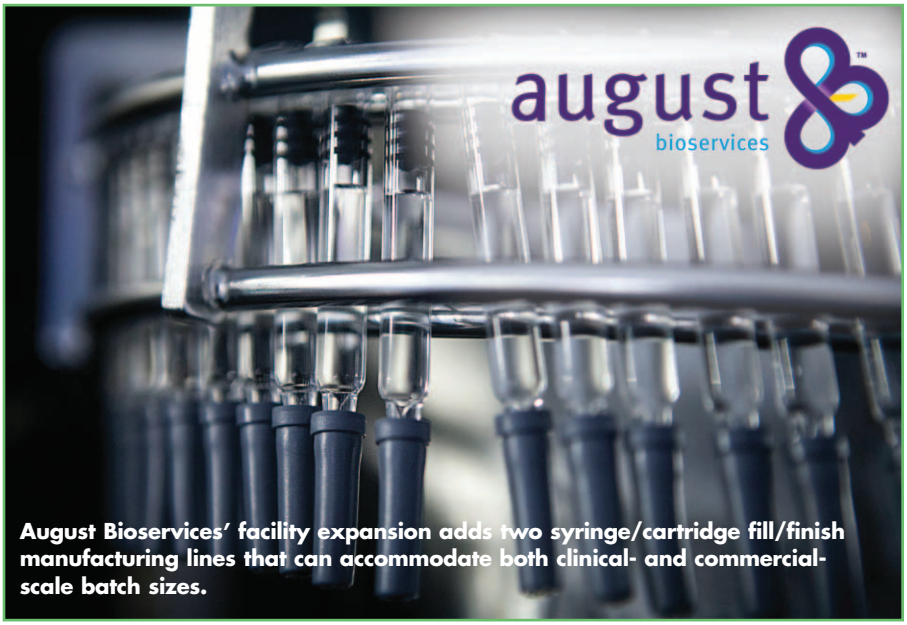
Finally, accelerating time to market while optimizing and derisking operations is of key importance for pharma companies that may also rely on contract manufacturing organizations for performing the final filling steps. Primary packaging's functionality can be a source of risk for compatibility with filling lines, and therefore a potential barrier to efficient industrialization. "Aptar Pharma's PremiumCoat® is compatible with both vent tube and vacuum technologies, enabling operational flexibility while facilitating the choice of primary packaging and CMO for pharma partners," Ms. Raynal-Olive says. "PremiumCoat 1mlL and 1-3mL plungers help derisk the primary packaging selection process so that our pharma partners can focus on their drug development."

August Bioservices: One-Stop-Shop Fill/Finish

August Bioservices develops and commercializes sterile injectable products. An integrated scientific and manufacturing team are on site and under one roof, making the company a one-stop-shop for clients in early drug development through clinical trials and commercial launch, says Ryan Downey, Director of Customer Operations, Commercial Development, August Bioservices.

Additionally, he says the company offers a flexible fill/finish platform that accommodates a range of prefilled syringe sizes, up to 60mL. "Our fill/finish capability, combined with an on-site analytical services platform that includes extractables and leachables, allows August to accelerate the understanding of compatibility for new drug products, evolving primary container designs, and materials of construction."

A recent expansion will enable August to offer drug development and manufacturing capacity later this year and into 2023, comments Mr. Downey. "Availability of capacity continues to be challenging for innovators attempting to address unmet medical needs, including COVID-related therapies. This is particularly difficult for



August Bioservices' facility expansion adds two syringe/cartridge fill/finish manufacturing lines that can accommodate both clinical- and commercial-scale batch sizes.

companies who are seeking small- to mid-size batch scale and/or have complex formulation and manufacturing requirements."

BD Medical – Pharmaceutical Systems: Collaborations Lead to Improved Product Development

Since 2010, BD Medical - Pharmaceutical Systems has conducted more than 80 human factors studies to ensure usability of its drug delivery solutions. Its portfolio features prefilled syringes for administration of injectable or nasal vaccines, as well as integrated devices and systems that can deliver biologics across a range of volume and viscosity levels for treating chronic conditions. The company is also focused on finding solutions for sequentially injecting two liquids with a single plunger push. In fact, BD filed a patent for a system made of a regular robust prefilled syringe that enables such sequential injection thanks to a redesign of a plunger stopper – involving no costly or fragile by-pass system, says Marie-Liesse Le Corfec, Head of Global Portfolio Marketing, BD Medical - Pharmaceutical Systems.

BD also believes connectivity is the future of drug delivery devices and is developing a connected product capable of capturing and transmitting injection-related data. The device will be an optional upgrade of the BD Ultrasafe Plus™ Passive Needle Guard and is intended to support decentralized and hybrid clinical trials. "The product will address patient needs, CROs, and study sponsors for a safe, easy-to-use self-injection device that automatically captures reliable, high-quality, and time-stamped data about the injection event from the patient (who may be self-injecting remotely) to the trial's selected electronic platforms," says Ms. Le Corfec.

BD recently teamed up with industry-leading partners in tagging and traceability technologies to develop syringe-specific traceability solutions integrating in broader Pharma 4.0. systems. "By supporting anti-mixup-controls, reconciliation or root-cause analysis, monitoring of time out of the cold chain, and manufacturing data integration into machine learning systems, this solution is meant to assist increasingly stringent manufacturing lines quality controls and audits while enhancing productivity," she says.

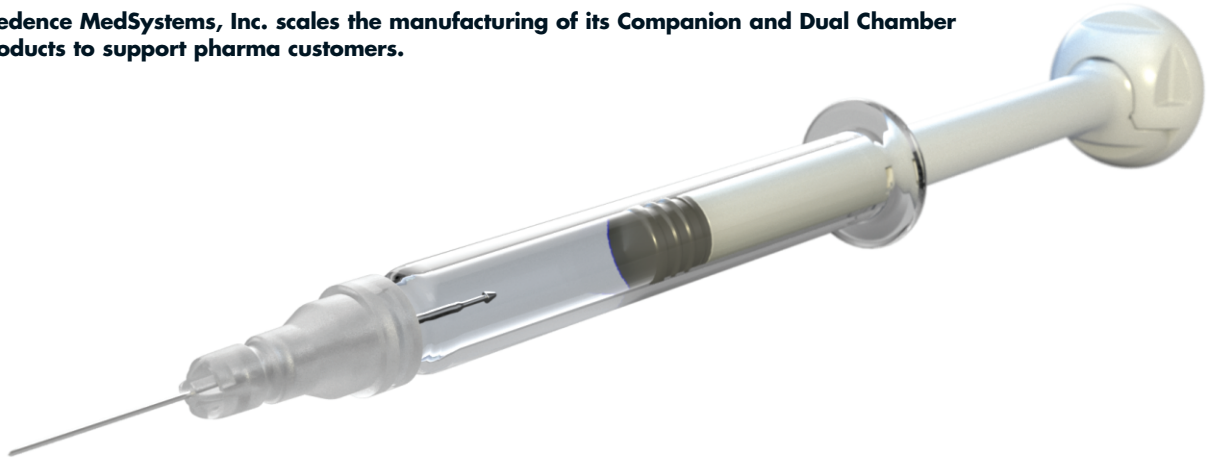
The company has also partnered with pharmaceutical and biotech companies to develop and produce innovations that enable new drug delivery needs. One biotech company developed a case study on how early collaboration, including needs and information sharing, can give the innovation timeline an earlier start and lead to initial launch readiness in the desired device configuration, working with BD specifically on co-development of the BD Neopak™ XtraFlow™ Glass Prefillable Syringe.

Ms. Le Corfec says: "This early-stage collaboration helped BD develop the right product to meet the drug's needs (higher viscosity, larger volumes, reduced needle anxiety, a single dose that's easy to inject, and well tolerated by patients). This avoided the need to add an additional loop in the design process to adjust to unmet needs. This process also gave the biotech confidence in the technology early on, as they were involved in the design process."

Credence MedSystems, Inc.: Solving Unmet Needs in Injectable Delivery

As Credence MedSystems scales its manufacturing capacity for its

Credence MedSystems, Inc. scales the manufacturing of its Companion and Dual Chamber products to support pharma customers.



Companion® and Dual Chamber product lines, John A. Merhige, Chief Commercial Officer, Credence MedSystems, Inc., says pharma companies are provided improvements in usability, safety, waste-reduction, sustainability, and operational efficiency – without having to reengineer processes or introduce undue risk.

Credence recently announced a successful $39.9 million funding round that included strategic investments from Novartis and Molex Ventures, as well as a strategic collaboration with Phillips-Medisize, a Molex company. Those collaborations have contributed to Credence's implementation of a flexible clinical manufacturing line that will produce up to 500,000 units per year of various configurations of the Companion and Dual Chamber product lines. Expected to be up and running later this year, this manufacturing capability will enable Credence to supply sufficient volumes to support development efforts, including stability studies and machine evaluations, as well as for human-use production for clinical study supply and eventually smaller volume commercial applications, explains Mr. Merhige.

The Credence Companion provides pharma manufacturers and their end users end-of-dose cues and automatic needle retraction. "User studies performed by Credence and its pharma customers document high user preference for the Companion while the integrated approach improves operational efficiency for pharma manufacturers by eliminating secondary assembly processes and the associated waste and cost," he explains. "In addition, Companion's streamlined design prevents premature activation of the safety mechanism, again eliminating waste and addressing regulatory concerns, and achieves a less impactful environmental footprint. Compared to conventional safety approaches, Companion uses 38% of the plastic, reduces the weight of added components by 58%, and occupies 33% of the volume post-use, helping pharma achieve corporate sustainability goals."

The Credence Dual Chamber Reconstitution Syringe simplifies the delivery of complex drug products, enabling less experienced users to safely and correctly administer medication. "As delivery of injectables moves from formal healthcare settings to the home, pharma developers face the challenges of achieving liquid-stable formulations."

The Dual Chamber system maintains separation of components during storage, offering a safe and friendly experience, he adds. "Simplified mixing and injection, combined with passive needlestick protection, minimizes time, complexty, and risk of dosing errors and contamination, while improving safety and usability."

Additionally, the platform employs the use of conventional commercially available syringe barrels and stoppers, allowing use of syringes ranging from 1mL to 20mL, glass or plastic barrels, and pre-attached needles or luer lock needleless front ends.

DALI Medical: Needle Safety Promotes Self Injection

DALI Medical offers a range of advanced injectable drug delivery devices and service development solutions from concept to commercialization. Its safety-engineered, patient-centric approach provides enhanced safety and ease of use for commercial trials and commercial drugs, explains Ziv Cahani, Vice President Business Development and Marketing at DALI.

DALI Medical's SAN (Safe Auto Needle) drug delivery devices increase safety, ease-of-use, and convenience, with features such as automatic needle insertion, passive automatic sharps

DALI Medical Devices' novel safety needle is a customized version of SAN-Light, launched both in the EU and US.

protection, a fully hidden needle along the whole injection process, and manual control of injection speed, Mr. Cahani explains. Additionally, the SAN-L is a passive safety and automatic needle-insertion device compatible with luer lock syringes, while the SAN-P is an automatic needle-insertion safety syringe for staked needle prefilled syringes.

Dual-chamber syringes can be integrated with DALI's SAN passive safety needles. Mr. Cahani says that one European pharmaceutical company has selected a DALI dual-chamber syringe for a new drug, and the product is expected to be launched in 2023.

"Our dual-chamber syringes, primarily targeted to healthcare professionals, and dual-chamber pens, offer highly intuitive usability that are ideal for self-injection," he says. Both solutions are available in a choice of configurations, enabling drug manufacturers to fit the syringe or pen to their specific drug and patients' preferences. For example, one of DALI's dual-chamber syringes is specially designed to ensure correct mixing of the two components.

DALI's SAN-Light single-use passive safety needle is being used by UK-based ADVANZ PHARMA for its Mytolac®/Myrelez®, a generic Lanreotide drug product launched in 2021. SAN-Light is connected to a prefilled syringe.

DALI also offers injection connectivity. The DALI SYNNECT connected injection solution incorporates sensing and connectivity technologies to accurately measure the administered drug's data and transmit it, enabling remote healthcare monitoring.

Eitan Medical: A New Era of Patient-Centric & Pharma-Minded Self-Injection

Even prior to Covid-19, a constant challenge associated with moving care to the home has been in maintaining patient compliance and adherence to treatment regimens and ensuring quality healthcare outcomes. As a result of the growing need for homecare solutions, the need for patient-centric self-administration devices has become a priority.

Additionally, new biologic-based drugs will be brought to market in the next decade, believes Dr. Andrei Yosef, General Manager of Pharmaceutical Solutions at Eitan Medical. "While introducing significant therapeutic benefits, their associated drug delivery challenges need to be addressed," he says. "With higher viscosities and larger volumes than chemically synthesized drugs, many of these biologic medications are expected to require an alternative delivery system to traditional hand-held injectors, limited to 1-2mL of liquid."

Eitan Medical Sorrel™ – Wearable Drug Delivery Device.

In parallel, some of these biologics are expected to launch in lyophilized form, requiring drug reconstitution prior to administration. This adds another level of complexity to the administration process and poses an additional barrier to self-administration.

Device solutions addressing both the shift to homecare, together with the challenges described above, include infusion pumps, reconstitution systems, dual-chamber syringes, wearable injectors, and more. However, for lyophilized biologics requiring dosages of above 2mL, a wearable drug delivery device that allows for reconstitution prior to administration would be ideal, says Dr. Yosef.

Eitan Medical's Sorrel™ wearable drug delivery platform features a variety of configurations based on a patented pumping mechanism and UV technology. The device is designed for easy and efficient subcutaneous, self-administration of large-volume and high-viscosity medications for use in homecare environments, he explains. "Eitan Medical is working to further expand the Sorrel offering to lyophilized medications, allowing the drug reconstitution process to occur inside the Sorrel device. By simplifying the reconstitution process, which currently is very cumbersome and generally involves multiple accessories, patient compliance and adherence to medication regimen may be better positioned for success."

He continues: "Furthermore, as pharmaceutical companies usually require long lead times to transition their

drug product from one primary container to another, the Sorrel device's primary container agnostic feature offers quick turnaround times for development of one primary container-based device to the next, skipping the lengthy transition process, and conforming to the primary container of Eitan Medical's pharma partner's choice. This allows pharmaceutical companies to go to clinic faster with the primary container they generally have available. By providing a wearable solution adaptable to multiple dosage forms, in a ready-to-use, prefilled and pre-loaded device, the Sorrel platform offers both a patient-centric and pharma partner-focused solution to the drug delivery market needs."

Emergent CDMO's new aseptic fill/finish lines offer flexible capabilities for clinical to commercial viral and non-viral drug products.

Emergent CDMO: Flexible Capabilities from Clinic to Commercial

Emergent CDMO offers a comprehensive range of drug product formulation and aseptic filling in vials and prefilled syringes, in various configurations, to address both viral and non-viral manufacturing needs – from early-stage clinical to late-stage commercial products. Emergent also offers cGMP lyophilization in conjunction with its fill/finish capabilities. "We can support biopharma innovators' needs for a range of platforms and technologies, including mammalian, viral, plasma protein-based biotherapeutics, and vaccines," says Nithin Stephen, Director, Commercial Development – Drug Product, Emergent. "We have experience working with viruses – recombinant, live, and live-attenuated – for the development and manufacture of vaccines and therapeutics."

Emergent has been enhancing its drug product aseptic fill/finish capacity and capabilities at several sites. New flexible fill lines offer aseptic fill/finish processing, which allows for more product batches in smaller quantities, while addressing regulatory uncertainties, Mr. Stephen explains. This year, the Camden facility (drug product manufacturing site in Baltimore, MD) began manufacturing operations with a groninger® FlexPro 50, which provides sterility with minimal line interventions and interruptions through the utilization of isolator-based technology for aseptic processing of ready-to-use (RTU) pre-sterilized syringes, cartridges, and vials. The line can support liquid or lyophilized products.

A viral drug product facility in Rockville, MD, is currently undergoing a 58,000-sq. ft. expansion, which includes a state-of-the-art high-speed fill/finish line, the groninger INTEGRA, with fully integrated isolator technology, Biosafety Level 2 (BSL2) capabilities, and an automated inspection, labeling, and packaging line. Mr. Stephen says this will enhance Emergent's capabilities in large-scale fill/finish manufacturing of viral biotherapeutics and vaccines.

Finally, a development and manufacturing site in Winnipeg, Manitoba, Canada, houses a Vanrx® SA25 Aseptic Filling Workcell, providing sterility assurance through a fully automated vial handling, filling, and stoppering process, designed to minimize line losses. "The Vanrx utilizes closed, robotic technology to support the production of non-viral next-generation therapies," he says. "Its flexible design base makes the Vanrx ideal for supporting high-value, small-batch size medicines."

Emergent recently supported a pharma client in achieving a successful prefilled syringe/parenteral program by expediting and solving challenges during the tech transfer process for a small-scale mRNA drug with minimal unfrozen hold time. The client asked for two fills to be com-

pleted within two months from the project kick-off, requiring Emergent to complete filling and packaging activities on the Vanrx Aseptic Filling machine within one month of project initiation. The client stressed the importance of freezing their product within 48 hours of starting formulation, which was key to the success of their therapy, Mr. Stephen explains. "Our Manufacturing Science &Technology, fill, and packaging teams worked together to successful complete the engineering and GMP fills on time. Of note, the formulation, filling, inspection, packaging, and freezing process were completed within seven hours during the engineering fill. Similarly, the GMP fill was completed within 29 hours, which allowed the product to be released on time to support toxicological and clinical studies, helping the client achieve their tight turnaround time."

Gerresheimer: Drug Packaging & Injectable Delivery

Gerresheimer is a solution provider for drug packaging and drug delivery systems for the injectables/parenteral market. Its portfolio includes glass and plastic vials and syringes, as well as drug delivery devices and autoinjectors. Its core competency is in fully automatic large-series production and in the manual and semi-automatic small series production of complex and technically sophisticated drug delivery systems.

"This broad portfolio enables us to offer customers a solution that really fits their active ingredient," says Stefan Verheyden, Global VP Gx Biological Solutions at Gerresheimer.

Gerresheimer recently introduced a digital tool that guides users intuitively through six targeted questions about specific characteristics of their pharmaceutical product that needs to be packaged, before offering a selection of appropriate solutions from the company portfolio. Mr. Verheyden explains that the guide uses a proprietary algorithm to filter through more than 1,500 pharmaceutical products based on the information provided by the user.

Some of Gerresheimer's products are:

- Gx InnoSafe syringe with an integrated passive safety system to prevent unintentional needlestick, as the needle is fixed in a sleeve after use. A special feature of the Gx InnoSafe syringe is that it can be processed on all existing filling lines without any additional preparation or assembly steps.
- Gx RTF ClearJect – prefillable polymer syringes are made of high performance Cyclic Olefin Polymer, making it suitable for use as primary packaging for sophisticated medications, especially for sensitive biologicals, biosimilars, and biobetters, but also e.g. hyaluronic acid applications. The dead volume in the polymer syringe is also minimized, reducing overall waste of costly drugs.
- SensAIR is an on-body drug delivery system that can deliver drugs of higher viscosity, such as monoclonal antibodies (mAb).
- Gx RTF injection vials are made from Type I borosilicate glass and meet all current requirements of the applicable ISO standards and pharmacopeias (USP and Ph. Eur.). They are manufactured in accordance with cGMP, washed in a cleanroom, packed in trays or in nests and tub, and sterilized.
- Type II glass is a form of soda-lime glass, also called soda-lime-silica glass. Type II glass is subject to a special internal surface treatment process that makes its surface less prone to leaching caused by alkaline solutions and is a possible option for most parenteral drugs.

Haselmeier: Self-Injection Pens Reduce Risk & Shorten Time-to-Market

Haselmeier™, the drug delivery device business division of medmix, designs, develops, and manufactures advanced drug delivery systems, such as pen injectors and autoinjectors, that are convenient and can be dosed with precision. Haselmeier has developed a range of ready-to-use platform devices for use with both cartridge and prefilled syringe primary packages. Its D-Flex™, D-Vario™, Re-Vario™ and new autoinjector systems are all meant for self-administration.

Haselmeier has also expanded its services to include pharmaceutical packaging to provide an integrated system for the delivery of finished combination products. Additional capability and capacity have been added in a new regional facility in the United States to reduce transport re-

The fully developed platform D-Flex™ as well as the Re-Vario™ and Re-Vario™ A from Haselmeier, a medmix brand.

quirements for drug products manufactured in America. "These fully developed platforms, such as D-Flex, allow for a more rapid development program for devices. This can then be used across multiple indications, simplifying both the development schedule and supply chain," says Terry O'Hagan, General Manager at Haselmeier.

In addition to improving self-administration, Haselmeier is focused on reconstitution. Mr. O'Hagan explains that new biologics drugs tend to be less stable in a liquid formulation, driving an increased need for dual-chamber systems where the drug needs to be reconstituted prior to injection by the patient. These systems tend to be more complex to use for a patient, requiring more steps to get the treatment ready for administration. "While Haselmeier has a range of reusable devices compatible with dual-chamber cartridges, one specific customer needed a disposable pen solution, which included an integrated reconstitution system with multiple dose volumes available to the patient," he says. "Each device would then only deliver a single dose."

Haselmeier leveraged its D-Flex disposable pen technology, integrating an in-pen reconstitution system to create the needed device. Each pen has four distinct doses available for patient selection based on the volume requirements. "We will leverage our expanded assembly capability and deliver the finished device to the customer's packaging facility," Mr. O'Hagan says. "This solution provided the needed device functionality while consolidating the supply chain for global distribution."

Medical Engineering Technologies Ltd: Testing for Confidence

Medical Engineering Technologies delivers combination device batch release and design validation testing. "There is a lot of physical, chemical, and stability testing to be done, whether for a clinical trial or direct regulatory submissions," says Mark Turner, Managing Director and President of Medical Engineering Technologies Ltd. "Developers of new formulations and devices need confidence when they make these submissions. You don't want delays and repeats at the end of your project. So, the test programs and protocols need to be well designed and executed while working against the clock."

As a testing company, Medical Engineering Technologies has seen a variety of multi-chamber devices. But Mr. Turner says they do pose some validation challenges. In particular, it is hard to measure leaks between chambers and the efficiency of mixing when the dose is activated. Interactions between the drug and container can also be complicated by the migration of materials. "We are developing tests to detect any stopper movement in storage or transport (particularly air transport), any premature mixing, and to assess the mixing efficiency as part of the dose accuracy testing," Mr. Turner says.

One particularly thorny issue is the Reference Listed Drug (RLD) comparison. This is meant to show that a biosimilar is equivalent to an RLD in all ways, including the physical characteristics of the delivery device. He says: "Any test program will always require deep thought about how to minimize the number of RLD samples required for testing."

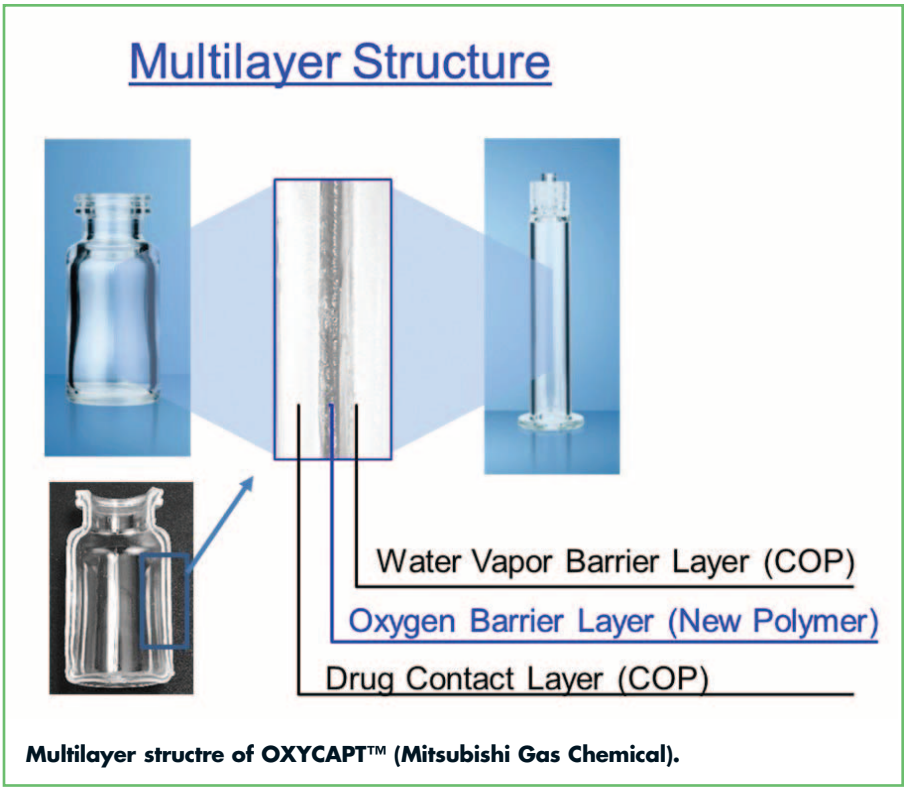
Meridian Medical Technologies: Seamless Parenteral Manufacturing

Meridian Medical Technologies is an integrated CDMO that takes complex sterile products from concept through industrialization to commercialization, offering both parenteral sterile filling and autoinjector manufacturing. "Every aspect of parenteral manufacturing is complex," says John Wilmot, Senior Director, Biomedical Technology Lead, Meridian Medical Technologies. "They include essential performance requirements for combination products, reliable and consis-

tent assembly, aseptic sterile filling of proprietary drug containers, manufacturing, and managing the vertically integrated supply chain."

Meridian has developed a technology platform that offers a drug delivery system that separates the drug API in a dry format from the solvent/diluent, and fully and automatically combines them during injection for optimal delivery, he explains. "We're looking into further developing this platform for freeze-dried products, which would add value for companies to apply this simplicity to biologicals, biosimilars or similar stability-sensitive molecules."

Meridian applies Human Performance through Human Factors to develop and enhance its manufacturing processes and make them as seamless and efficient as possible, Mr. Wilmot says.



Multilayer structre of OXYCAPT™ (Mitsubishi Gas Chemical).

Mitsubishi Gas Chemical: Plans to Supply Staked-Needle Syringes

Mitsubishi Gas Chemical (MGC) provides a multilayer plastic vial and syringe called OXYCAPT™. The product features an oxygen and ultraviolet barrier, high-break resistance, wide pH range tolerance, very low extractables, cryogenic-temperative resistance, and more.

MGC has also been developing staked-needle syringes. Equipment installed last year has been undergoing validation studies and will start supplying samples by the end of this year, says Tomohiro Suzuki, Associate General Manager of MGC.

MGC is also developing customized syringes. "As customizability is one of the plastic's features, MGC can help pharmaceutical or medical device companies achieve their successes," says Mr. Suzuki.

Nemera: Keeping Up with Subcutaneous Delivery

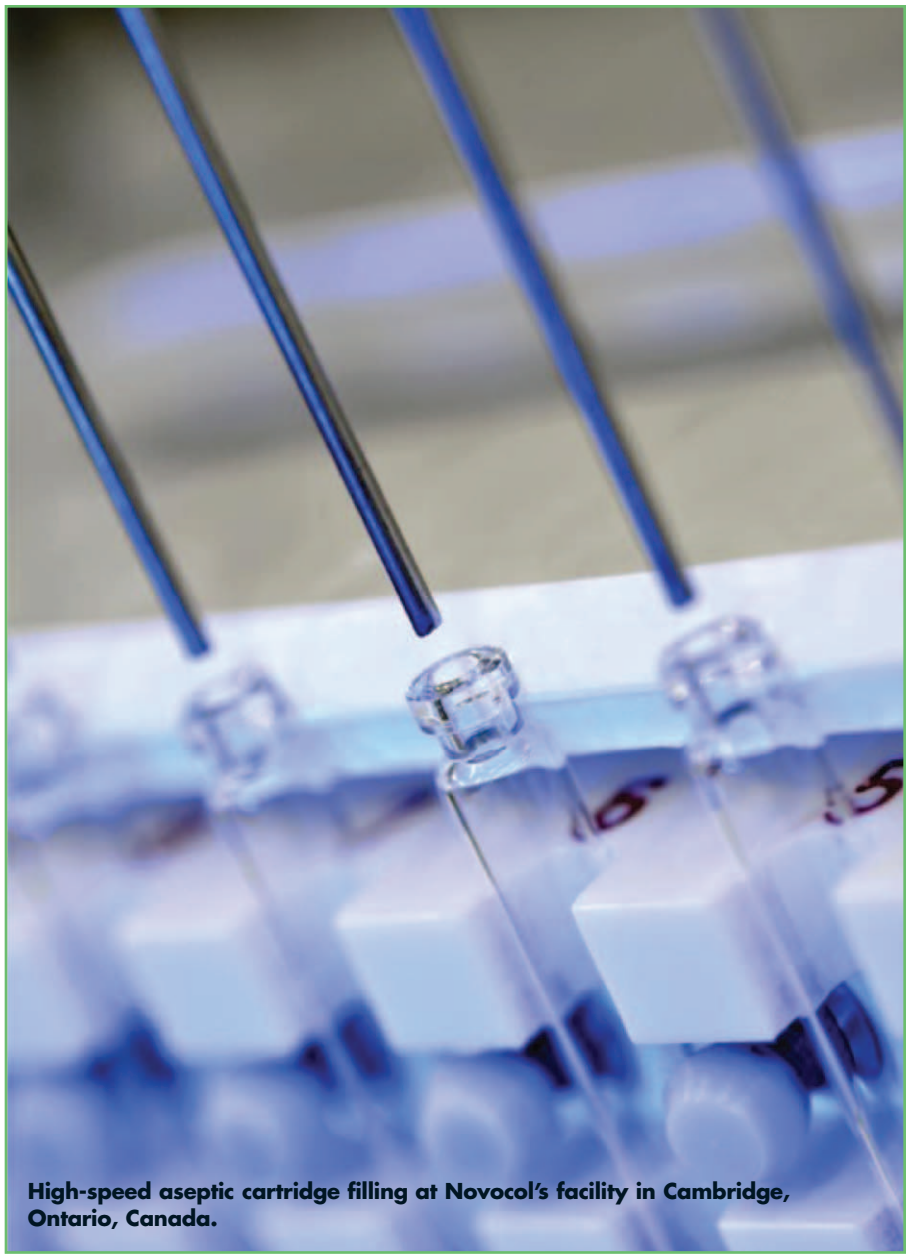
"With the rise of biologic and biosimilar formulations, and the increasing trend in self-administration due to the switch from intravenous to subcutaneous, a drug delivery device must be simultaneously robust and easy-to-use, as well as economically viable," says Cecile Gross – Global Category Manager, Parenteral, Nemera. "Nemera's offerings address the challenge of designing complex devices aimed at simple care. To accommodate a range of applications, a platform approach is a must."

The new Symbioze platform, for example, is designed to adjust to any pathology, targeted patient population, and drug posology according to therapy indications, she explains. Symbioze comprises a reusable main unit and a disposable prefilled drug container module. "It offers an ideal balance between the need to deliver advanced and complex formulations at high volumes," says Ms. Gross. "It is the perfect combination between design robustness, ease of use, connectivity, and sustainability for a seamless and enhanced injection experience."

Nemera's other product lines are all offered through a platform approach. For example, Safe'n'Sound® is a highly customizable passive safety device available in 1mL and 2.25mL formats, suitable for both skilled and lay users, to enhance the injection experience. It can integrate color, material or even overcap customization, as well as a Rigid Needle Shield (RNS)

puller to help with device handling, particularly for patient populations with dexterity issues.

Nemera also offers four platforms of reusable and disposable pen devices that are adaptable to treat various pathologies and are also customizable. Audrey Chandra – Category Project Manager at Nemera, explains how the reusable pen platform, Pendura AD, has been commercialized with several market references to treat different pathologies, including diabetes. Pendura AD offers automatic delivery with spring-driven movement, and an easily triggered side button actuator to allow the user's hand to be stabilized during injection time. In addition, the dial-back possibility prevents loss of insulin, and changing the cartridge is easy to perform, she describes.



High-speed aseptic cartridge filling at Novocol's facility in Cambridge, Ontario, Canada.

Novocol Pharma: Growing Demand for Cartridge-Based Products

Novocol Pharma is a CDMO specializing in turnkey sterile cartridge development, manufacturing, testing, and combination product assembly services. With more than 40 years of experience filling sterile injectable cartridges, Novocol is positioned to support cartridge-based programs. "The cartridge format is commonly integrated in a combination drug device product with a history of applications, including chronic diseases such as diabetes and emergency lifesaving applications such as anaphylaxis," says Eric Lee, Business Development Director, Novocol.

In response to growing customer and market demands, Novocol has invested in additional aseptic fill/finish and pen injector device assembly capacity. In fact, more than 50% of Novocol's programs are paired with a pen injector device. To support clinical and registration phase customers with a cartridge-based pen injector device, Novocol now offers device assembly services using an automated pilot-scale device assembly machine. The device assembly machine was installed and qualified in 2021 with capabilities to meet the specifications for market-leading press-fit style pen injectors.

In addition, Novocol has invested in 100% increased capacity in aseptic cartridge filling, which will be fully operational in the second half of 2023. This new line will offer similarities to the existing aseptic cartridge filling lines in terms of custom siliconization, precise plunger insertion depth controls, filling capability, and highly-potent API handling capabilities, allowing for ease of line transfer and risk mitigation for new and existing

customers alike. "With these investments in place, Novocol is well-positioned to support the growing demand for cartridge-based combination products," says Mr. Lee.

Oval Medical: Proprietary Technologies Improve Patient Experience

Intravenous novel targeted therapies, cancer treatment, and biologic drugs that were traditionally administered in hospitals are now benefiting from advances in formulation technology, enabling simpler and easier subcutaneous administration. There is also a well-documented trend towards reducing dosing frequency with longer acting injectables. These advances mean many targeted therapies and precision medicines can be potentially self-administered by subcutaneous injection at home. However, there are still viscosity and volume challenges that cannot be met with standard glass-based autoinjector systems.

Oval Medical is addressing this with the ArQ-Bios autoinjector platform, which features a modular capability to enable customization that works for both the patient and the formulation, ensuring patients can self-administer medicines outside of a healthcare setting," explains Barbara Lead, CEO of Oval Medical. ArQ-Bios is a high power, single-use modular autoinjector platform with the ability to deliver challenging high viscosity or large-volume dose options for subcutaneous delivery. This allows flexibility for formulation development, early engagement with the device, and reducing risk and time to the market."

Low- to medium-viscosity formulations under 100 cp can be delivered up to 10mL and high/ultra-high viscosities up to 10,000 cp can be delivered between 0.5-3mL. At a viscosity of 1000 cP formulation, ArQ-Bios can deliver 1mL through a 25G needle in less than 5 seconds. She says: "Owning and manufacturing the primary drug container allows integrated devices to be designed for patient needs."

ArQ Bios incorporates a proprietary hydraulic valve release mechanism that enables quiet and gentle activation of the device, even when the drug is pressurized at 300 bar. These features make ArQ-Bios an enabling technology for high-viscosity or large-volume applications.

Also proprietary is Oval's patented "cup seal and foil" technology, which is built around a high-pressure cyclic olefin co-polymer primary drug container. "The container can safely tolerate significantly higher pressure than glass, allows stronger springs, and enables the device to generate higher pressures than other market offerings," Ms. Lead says. "The design aims for a superior patient experience and reduced 'wet' injections due to highly consistent drug delivery times, independent of product age or manufacturing tolerances."

Owen Mumford Pharma Services: Disposable Autoinjector Platform

Owen Mumford Pharmaceutical Services introduced what it claims was the first autoinjector, Autoject 1, back in the mid-1980s. Since then, the company has produced autoinjectors in a variety of designs for multiple pharma companies. In the last year, Owen Mumford launched the disposable autoinjector platform, Aidaptus®, a two-step, easy-to-use small and discreet option for the patient to integrate into their regular routine. The needle is automatically deployed following depression of Aidaptus onto the selected injection site. The drug is then delivered in a separate phase controlled by a second delivery spring in the device. "This design helps to provide a consistent injection experience and also minimizes syringe breakage that may occur with high force

Owen Mumford's latest innovation is Aidaptus®, a platform disposable autoinjector offering next-generation benefits of flexibility and versatility.

springs," says Michael Earl, Director of Pharmaceutical Services.

Aidaptus is available in two base design options: a transparent body with an overwrap that can be printed and branded as required, or an opaque body with color customization choices. There also are options for window size in both designs either as a cut-out in the overwrap or different size molded windows in the opaque version. Both allow the window to be tailored to the required drug fill volume.

During development phases, through clinical trials and commercialization, parenteral drug formulations can go through a variety of iterative changes. This can pose problems when the drug requires a device, such as an autoinjector for delivery, as they are typically designed to deliver a set volume. Therefore, changes in fill volume or syringe size normally require design changes in the actual device and the associated validation processes and regulatory approvals. This can create complexity and risk in the development process. "At Owen Mumford Pharmaceutical Services, we looked to address this problem by creating a self-adjusting plunger in our Aidaptus disposable autoinjector," he explains. The plunger automatically adjusts to differing fill volumes and stopper positions, but also creates a critical gap between plunger and stopper to allow only a restricted level of rearward movement by the stopper. This ensures that container closure integrity is maintained during pressure changes that may occur during the supply chain and during patient use.

Aidaptus can accommodate both 1mL and 2.25mL prefilled syringes in the same base device, requiring minimal change parts. This means that the small size of the autoinjector, 165mm high and 18mm wide, is maintained irrespective of the syringe size, Mr. Earl explains.

As there can be changes in volume during drug development there can also be challenges with viscosity, particularly with higher viscosity formulations typically found with biologics. Aidaptus offers a choice of high and low power springs to adapt to varying viscosity drugs while helping to keep drug delivery time within an acceptable range for the patient. Aidaptus has been designed with the two sub-assemblies that fit together after the syringe insertion; the self-adjusting plunger then automatically moves into place to ensure an easier final assembly.

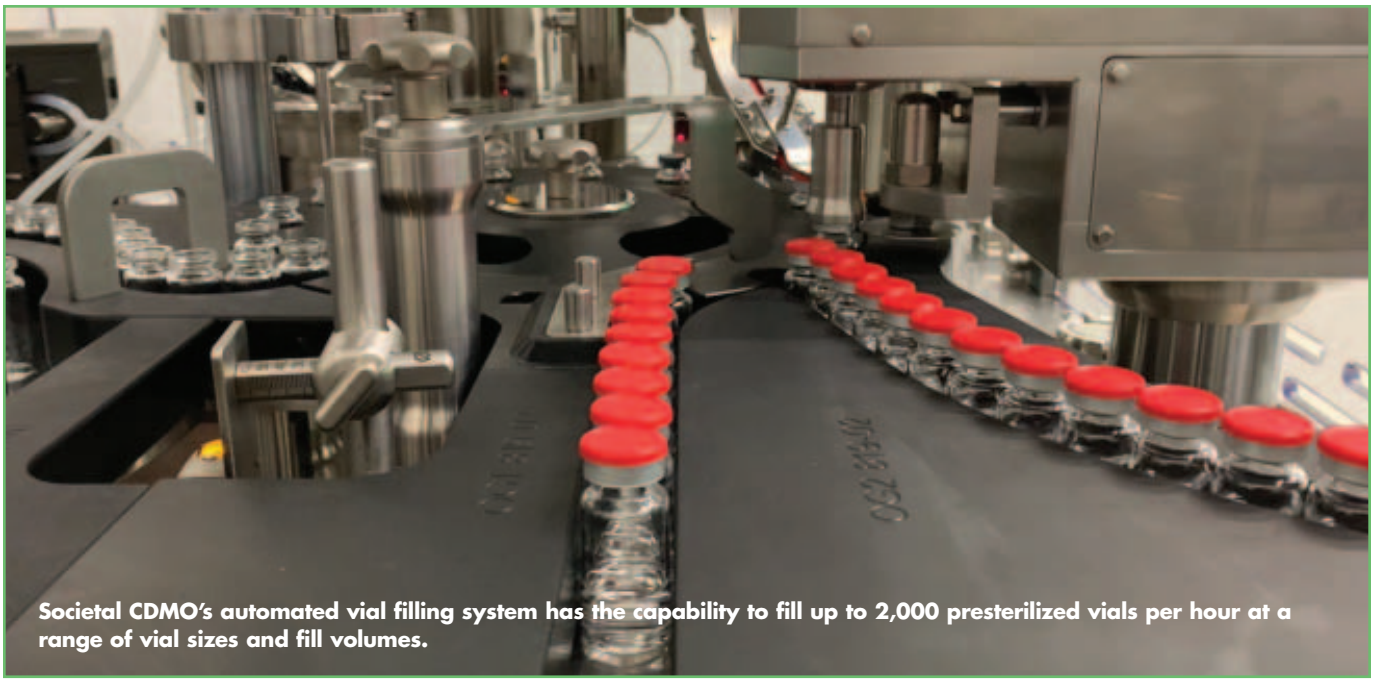
Recipharm: Addressing Common Drug Delivery Challenges

Recipharm designs, develops, and manufactures injectable drug delivery devices to the global parenteral market, offering a range of autoinjectors, assisted syringes, mixing systems, and other injectable technologies. One challenge these technologies address is delivery of high-viscosity formulations. For example, the Viscala® technology platform features the proprietary VapourSoft® delivery system for delivering highly viscous formulations from standard primary packaging by amplifying the force/pressure applied. "Using this technology, formulations with viscosities of up to several thousand centipoise (cps) can be delivered using fine needle gauges, increasing possibilities for our pharma company partners and putting patient comfort at the forefront," says Gemma Wood, Innovation Manager at Recipharm.

She describes how a customer approached Recipharm with a highly viscous formulation for delivery by autoinjector. The formulation reduced the dosing frequency required for the drug product, improving quality of life for patients and reducing overall healthcare costs, she says.

"The high viscosity of the formulation meant that it could not be delivered using standard autoinjector technologies and the customer did not want to use large gauge needles because of the impact on patient comfort and compliance. To address this issue, we developed an innovative, new autoinjector with force amplification that enables the highly viscous formulation to be delivered simply, easily, and with patient comfort in mind by using the finest needle possible."

Ms. Wood adds that Recipharm platforms also solve challenges such as the delivery of large volumes, and re-suspension prior to delivery. She specifically points to the Lila® technology platform, a combination valve and primary pack stopper. Lila Duo enables two liquid drug products to be filled into a single primary pack, keeping the two products completely separate until the point of administration and allowing them to be delivered sequentially from a single syringe. Lila Mix enables the products to be mixed or re-suspended immediately before delivery takes place.



Societal CDMO's automated vial filling system has the capability to fill up to 2,000 presterilized vials per hour at a range of vial sizes and fill volumes.

Societal CDMO: A Range of Parenteral Services & Offerings

Societal CDMO provides preformulation, formulation development, and fill/finish services across a range of parenteral product types, technologies, and phases of drug development. Societal's experience includes small molecules, and biologics (proteins, peptides, monoclonal antibodies, RNA, and pegylated molecules).

According to Robert Giannini, Vice President, Innovation, Societal CDMO, the company's formulation development and manufacturing team has been able to:

- Create a completely non-aqueous formula of an insoluble compound, which upon dilution with saline, provides sufficient time for the product to be administered without precipitation;
- Stabilize and subsequently manufacture clinical trial supplies of lyophilized product for highly labile pegylated molecules and mRNA/siRNA therapeutics; and
- Create a nanoparticulate form for an extended-release (up to 3 months) intramuscular injection.

Some of Societal's offerings include:

- Aseptic fill and lyophilization of true solutions: True solutions in vials prepared by sterile filtration (from small batches of 1 Liter or less to up to 500L for clinical materials, up to ~10,000 vials per shift, 2mL to 50mL vials, Phase I/II) with 100% weight check and with or without Nitrogen overlay; and Sterile lyophilization (from small batches of 100 to 1000 vials for clinical materials, up to ~9,000 vials per load at the 10mL vial size, the number of vials per load varies with vial size from 2mL to 50mL, Phase I/II). Controlled nucleation technology is available.
- Microspheres/nanoparticles for injection for terminally sterilized product: Prepared by solvent emulsification followed by solvent removal, size segregation, and lyophilization (small batches of about 50g to 500g of finished microspheres corresponding to about 100 to 1000 vials, Phase I/II); prepared by ball milling with surfactants followed by lyophilization or aseptic filling into vials (small batches of about 50g to 500g of finished microspheres corresponding to about 100 to 1000 vials, Phase I/II).

Stevanato Group: PFS for Biologics Delivery

Stevanato Group provides a full range of products and services for injectables, supporting several therapeutic areas, with a variety of prefillable syringe systems to cater to different drug formulations and applications. A good example is biologics, explains Silvia Gallina, Product Management Specialist, Syringe Platform, Stevanato Group. "Because most biologics' primary administration route

Prefillable syringe systems at Stevanato Group can cater to different drug formulations and applications.

remains parenteral, with a significant increase of the subcutaneous type, PFSs have gained strong acceptance as the preferred delivery system."

Stevanato Group's Nexa® product lines, for example, have been designed specifically to meet the requirements of high-viscous formulations and drugs sensitive to specific elements, such as tungsten. In addition, SG Nexa can be easily integrated into manual active and passive needle safety systems and automatic drug delivery devices, such as spring-based autoinjectors.

With a growing trend towards biologic drug products, Stevanato Group's focus is on mitigating drug container stability risk for such drugs, which have higher chemical sensitivity, lower stability, and strong fluid dynamic characteristics (i.e., high viscosity). "Most parenteral packaging components require surface treatment or lubrication to improve their processability and functionality," she says. "Silicone oil is often used, but it can result in some unwelcome interactions with highly sensitive drug formulations. Specifically, silicone migration can lead to the accumulation of sub-visible particles, which may cause non-compliance with pharmacopeias and potentially registration failure as product safety and efficacy are compromised. In addition, a protein can adsorb at the silicone oil interface and lead, over time, to protein denaturation."

Furthermore, she says excipients used in formulations can negatively affect different container materials and lubricants. The performance of autoinjectors could be compromised as it could lead to variations in glide force and an incomplete dose being delivered. In addition, silicone droplet accumulation or migration may result in a higher reject rate during the final product release, which will have an impact on productivity and the total cost of ownership.

Stevanato Group developed its Alba® platform with new coating technology. "A cross-linked silicone chain leads to improved layer structure using covalent bonds, increasing the connection force between the silicone and glass while retaining lubrication performance," Ms. Gallina says. "A thin, permanent silicone coating is created, reducing sub-visible particles release."

Terumo Pharmaceutical Solutions: Meeting Ophthalmic Drug Delivery Challenges

Terumo Pharmaceutical Solutions (TPS) designs, develops, manufactures, supplies, and manages projects associated with polymer-prefillable syringes and injection devices. TPS products and services are focused on injectable drugs that include syringes, hypodermic needles, infusion sets, and CDMO fill/finish services.

"Compared to a vial, a prefilled syringe can reduce the number of steps to administer injectable drug and help avoid dosage errors," says Katsuyuki Takeuchi, Associate Product Manager of Terumo Pharmaceutical Solutions. "PFS are specifically designed to meet the stringent requirements of certain applications such as ophthalmic, biologics, and dermal fillers.

Terumo also has an industry-wide network to integrate PFS into drug delivery devices like autoinjectors and safety devices. Terumo has capabilities and expertise to offer customized solutions to meet challenges of a particular drug or therapeutic area.

Terumo has been working on ophthalmic drug PFS development programs with customers. "There is an

Terumo is patient-centric in thinking and customer-centric in actions.

increasing number of patients that require ophthalmic drugs administered by intravitreal injection, triggered by the rapidly aging global population," says Mr. Takeuchi. "These ophthalmic drugs are administered by intravitreal injection, however, there are still several unmet challenges to design a prefilled syringe for safe administration of ophthalmic drugs."

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

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

Vetter Pharma Intl. GmbH: Dual-Chamber System for Sensitive Compounds

Vetter is a family-owned, globally operating CDMO with services that range from early-stage development support, including clinical manufacturing, to commercial supply and numerous packaging solutions for vials, syringes, and cartridges. Vetter supports pharmaceutical and biotech companies in the development phases, in the filling of small- to large-scale batches, and in the packaging of their complex compounds. Approximately 80% of the compounds it handles are biologics. In the field of clinical manufacturing, Vetter offers process development, clinical trial manufacturing, technology transfer, regulatory support, and analytical services. For commercial manufacturing, services include fill/finish, regulatory support, analytical services, and life cycle management. Both primary and secondary packaging, as well as device assembly, are realized.

Vetter offers dual-chamber systems in its service portfolio: Vetter Lyo-Ject® dual-chamber syringe as well as V-LK® dual-chamber cartridge. Both systems are suitable for sensitive compounds. "Our patented syringe and cartridge technologies allow a freeze-dried API and a diluent to be prefilled and stored separately for easy reconstitution prior to administration," explains Carsten Press, Senior Vice President Key Account Management, Supply Chain Management and Marketing, Vetter Pharma International GmbH.

Mr. Press adds that the dual-chamber systems combine multi-faceted advantages. For the biopharma company, they offer low residual volume and reduced API loss with a faster time-to-market. The dual-chamber cartridge is also com-

The dual-chamber syringe system, Vetter Lyo-Ject®, combines multi-faceted advantages.

patible with multiple pen systems. Both systems offer high product security and extend storage periods for sensitive drugs.

"Through their design, dual-chamber systems afford improved shelf life and options for life cycle management," he says. "For patients, dual-chamber systems offer a safe, comfortable, and user-friendly design that allows for precise dosing every time with a reduced potential risk of needle injury as well as a lower risk of contamination compared to the use of vials. Our closure systems also make them tamper-evident. And, because they have prefilled substances in both chambers, reconstitution errors are significantly reduced." ◆

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REGENERATIVE MEDICINE

Delivering on the Promise of Regenerative Medicine in Type 1 Diabetes

By: Thomas Donner, MD

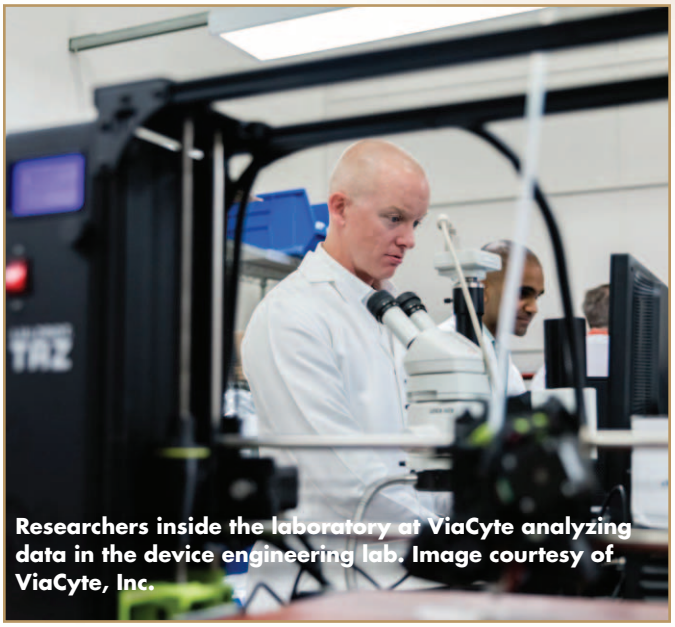
INTRODUCTION

Each day is a challenge for the 1.4 million US adults and 200,000 youth under age 20 living with Type 1 diabetes (T1D).[1,2] Their need to frequently monitor glucose (blood sugar) levels and adjust insulin doses to counter the effects of food, exercise, and physical and mental stress is often arduous and exhausting. In the US alone, 64,000 people are newly diagnosed with T1D each year, and that number is on the rise.[2]

Among youth under age 20, T1D cases increased by 21% between 2001 and 2009, while annual incidence rates increased by 1.9% from 2002 to 2015.[3-5] An estimated 5 million people in the US are expected to have T1D by 2050, including nearly 600,000 youth.[3] Moreover, the accompanying financial impact is significant: T1D-associated healthcare expenditures and lost income are estimated at $16 billion annually.[4] Clearly, T1D represents a major public health problem in urgent need of solutions to better manage or cure the disease.

CHALLENGES OF LIVING WITH T1D

Since insulin was discovered in 1921, people with T1D have benefited significantly from advances such as faster-acting types of insulins, continuous glucose monitors, and automated insulin pumps. These tools have enabled less cumbersome, safer, and more physiologic insulin replacement and diabetes control. Unfortunately, most individuals with T1D still struggle with the challenges of managing their disease, including the need for multiple daytime glucose checks and frequent insulin dose adjustments to



Researchers inside the laboratory at ViaCyte analyzing data in the device engineering lab. Image courtesy of ViaCyte, Inc.

counter the effects of food, physical activity, and both physical and psychological stress on glucose levels. Moreover, because each day is different, insulin requirements vary from day to day.

Many individuals find it challenging to follow an intensive diabetes management regimen and therefore experience suboptimal glycemic control. When their diabetes is uncontrolled, patients are predisposed to acute consequences, such as severe hyperglycemia (high glucose), which can lead to compromised immune function, frequent urination, dehydration, vision problems, and other symptoms. In cases of missed or markedly inadequate insulin dosing, consequences can be more severe, leading to vomiting, acidosis, coma, or even death. When T1D is uncontrolled in the long-term, patients are at high risk for complications such as nerve damage, kidney injury and failure, vision loss, and amputations. They also have a three-fold greater likelihood of a

heart attack or stroke compared to those individuals without T1D.

On the opposite end of the glucose spectrum, insulin also is commonly associated with hypoglycemia (low blood glucose levels), which also can be quite symptomatic, leading to coma, seizures, and death when levels fall severely low, and are unrecognized and untreated. Up to 40% of patients with T1D have hypoglycemia unawareness, meaning they become physiologically unaware of low glucose levels.[6] Hypoglycemia unawareness is particularly concerning because these individuals have a six-to-seven-fold greater risk of experiencing a severe hypoglycemic event requiring assistance from others to bring glucose levels back to normal.

One large study found that 83% of people with T1D reported a hypoglycemic event within a 4-week period. Findings also showed a prospective rate of more than 73 hypoglycemic events/patient-year; 14.4% of patients experienced a severe hypoglycemic event with annual rate of 4.9 events/patient-year and a severe hypoglycemia hospitalization rate of 0.237 events/patient-year.[7] Even more concerning are reports that as many as 4% to 10% of patients with T1D die of hypoglycemia.[8]

Although pancreas transplants can normalize glucose levels, these interventions subject patients to the risks of major surgery and require them to have lifelong immunosuppressive therapy. Moreover, these organs are in short supply. Patients with T1D are therefore in need of novel interventions that will provide a safe and effective alternative to current insulin replacement options. The field of regenerative medicine may well hold the key.

ViaCyte researcher thawing stem cells for expansion. Image courtesy of ViaCyte, Inc.

REGENERATIVE MEDICINE'S PROMISE

Insulin pumps and continuous glucose monitoring are helping improve the management of T1D but do not address the underlying biological driver of disease, namely the immune system's attack on insulin-producing pancreatic beta cells. Clinical trials designed to non-selectively interrupt autoimmune attack on beta cells have proven unsuccessful when doses well-tolerated by patients are used that do not effectively suppress immune system attack.

Regenerative medicine, led by advances in stem cell research and biomaterials, has the potential to restore the body's normal glucose regulatory system, offering promise in T1D treatment. These technologies, aimed at creating and implanting viable beta cells, could enable the tighter regulation of blood glucose levels. Once vascularized, these cells can monitor real-time glucose levels and rapidly adjust insulin delivery directly into the bloodstream versus patients injecting insulin into subcutaneous tissue, which can delay absorption. If successful, this mode of therapy could provide an adequate number of functioning beta cells to both prevent progression of any existing T1D complications and avoid treatment-associated hypoglycemia.

CADAVER ISLET CELL TRANSPLANT VIABILITY

Already, research has shown that islet cell transplants are a viable method of replacing the pancreas' insulin-producing beta cells in addition to alpha and delta cells that are responsible for glucagon and somatostatin production, respectively. Transplanted cadaver-derived islet cells show promise in improving outcomes for patients with T1D, potentially providing better glycemic control, preventing severe hypoglycemia and offering relief from the need for multiple daily insulin injections or pump infusions.[9]

Between 1999 and 2015, more than 1,000 patients received greater than 2,000 allograft infusions of cadaver islets.[10] About 90% of recipients were free of hypoglycemic events for more than 5 years, and more than 50% of recipients

Researcher viewing image of beta cells in a preclinical islet graft produced by ViaCyte. Image courtesy of ViaCyte, Inc.

had sufficient allograft insulin production over the same period to preclude the need for exogenous insulin replacement.[10] Despite these promising findings, however, only about 50% of transplant recipients achieve insulin independence at 1 year following completion of cell transplantation.[10] Although transplantation using cadaver-derived islet cells has demonstrated proof-of-concept for islet cell replacement therapy, there is a limited supply of these donated cells. In addition, like pancreas transplants, cadaveric islet transplants still require chronic immunosuppression.

ADVANCING THE FIELD

Scientists are exploring regenerative medicine approaches to improve insulin replacement and potentially cure diabetes. Their work focuses on differentiating stem cell lines into pancreatic endodermal cells that enable implantation into patients and provide a nearly unlimited source of cells. Researchers also are investigating various cell and delivery engineering techniques aimed at ensuring long-term survival of transplanted cells. The goal is to develop a delivery device that can protect these cells from immune system attack while also enabling the exchange of glucose, hormones, and other biomolecules. Immune evasion is critical because if the device's outer membrane is recognized as foreign, the body's immune response will generate an inflammatory reaction leading to scarring that may impair adequate vascularization of the implanted cells, limiting insulin secretion.

Investigators are exploring several types of approaches, including a pouch-like device about the size of a credit card that encloses and protects the cells or a device that enables engraftment, as well as a method of individually coating islet cells with a protective polymer.[11,12]

PROMISING FINDINGS FOR ENDODERM CELLS

Restoring normal glucose regulation requires an adequate number of insulin-producing beta cells, as well as alpha cells that produce glucagon and prevents glucose levels from dropping too low. Toward that end, researchers are evaluating a variety of approaches focused on realizing the potential of regenerative medicine therapies for T1D. One approach uses pancreatic endodermal cells produced from stem cells that differentiate to become both alpha and beta cells. Promising preliminary data from a clinical study of this approach were reported by the company ViaCyte in June 2021 at the annual American Diabetes Association (ADA) meetings.[13] In the study, subjects who were C-peptide negative at screening, indicating they were not producing insulin, received subcutaneous implants of encapsulated pancreatic endodermal stem cells.

Results from a Phase 2a clinical trial presented at ADA indicated that a patient was doing well with stimulated C-peptide levels up to 0.8 ng/mL (2.67 nmol/L) at 39 weeks.[13] Investigators also reported a 0.8% reduction in HbA1c from a baseline of 7.4%, as well as increased time in desired glucose range from 54% to 88% at week 42 in this research subject.[15] These results are promising, as C-peptide levels of >0.2 nmol/l become clinically meaningful, and clinicians consider >70% time-in-range to be an indicator of good diabetes control.[14,15]

FURTHER STEM-CELL RESEARCH

Other approaches using more mature pancreatic cells also are being evaluated in clinical trials. Vertex Pharmaceuticals, for example, launched a Phase 1/2 clinical trial using an islet product, immunosuppression, and intraportal cell delivery. Meanwhile, Seraxis has developed a stem cell islet product, likely to be delivered in a subcutaneous device, with plans to begin pilot clinical testing soon. Scientists are fo-

cused on determining the best method and location in which to deliver pancreatic cells, including various types of implanted devices and insulin release into patients' portal veins to more directly inhibit hepatic glucose production. This work is also evaluating a variety of biomaterials and engineered cells that may eliminate the need for immunosuppressants. An example is CRISPR-based, gene-editing techniques, with the potential of developing stem cells engineered to evade immune system attack.[16]

BUILDING ON INNOVATION

Although regenerative medicine and stem cell-based therapies are an emerging field, preliminary data are promising and warrant further development of these innovations. Technological advances over the past 5 years have demonstrated insulin secretion associated with improved glucose regulation following implantation of pancreatic endodermal stem cells. Further advances in stem-cell engineering, immune-evasion technologies and vascularization of implanted cells have the potential to generate novel therapeutics that could lead to reduced treatment burden for patients with T1D and infuse new energy into efforts at finding a cure. ◆

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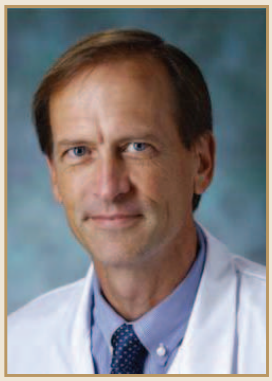
BIOGRAPHY



Dr. Thomas Donner is the Director of The Johns Hopkins Diabetes Center. He has been a clinical investigator in numerous NIH- and industry-funded diabetes research trials. He was a co-PI in the NIH-funded Veterans Affairs Implantable Insulin Pump Study, a Co-PI on the NIDDK-funded Diabetes Control and Complications Trial/Epidemiology of Diabetes Intervention and Complications (DCCT/EDIC) Study, and Co-PI for the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D). He has served as a PI for TrialNet, a multicenter, international consortium of investigators studying ways to prevent Type 1 diabetes and preserve insulin secretion in individuals with newly diagnosed Type 1 diabetes. He has also served as PI for DEFEND-1 that used otelixizumab to try to prevent loss of islet cell function in new onset type 1 diabetes, and was a PI for a study involving the first subcutaneous implants of encapsulated pancreatic endodermal stem cells into patients with type 1 diabetes. Dr. Donner is currently collaborating with immunologists at Johns Hopkins on the characterization of a newly discovered immune cell that expresses both B and T cell receptors that may trigger type 1 diabetes.

Drug Development
EXECUTIVE

Shawn Cain, MS

SVP, Development & Manufacturing

PCI Pharma Services

PCI Pharma Services: Broadening Our Biologics Footprint, Together

At the end of 2021, PCI Pharma Services acquired Lyophilization Services of New England, Inc. (LSNE), expanding PCI's breadth of services as a global CDMO, building on its expertise in specialty manufacturing and packaging at both clinical and commercial scale. Already perceived as a pioneer in the packaging of biologics, the addition of LSNE cements PCI's reputation as a leading global CDMO providing an integrated solution to clients across the entire drug product lifecycle from development to commercialization, meeting the demands of the ever-growing biologics market and bringing life-changing therapies to patients faster.

Drug Development & Delivery recently spoke with Shawn Cain, SVP Development & Manufacturing at PCI Pharma Services, to discuss the recent acquisition, the opportunities this presents to Biopharma companies, and the current trends in the sterile fill-finish industry.

Q: How has the recent acquisition process of LSNE been?

A: Thus far, the acquisition has been relatively seamless. Company cultures, employees, and processes are integrating smoothly as our strategy has been to focus on our customers and the patients we serve through aligned objectives. Both companies are working together to demonstrate the breadth of the new offering as this is definitely a case of the sum of the parts proving to be of more value than the individual components. It is worth mentioning that we have just completed the first 100 days of our integration plan, and we have successfully achieved each one of our milestones.

Having worked within LSNE for nearly 10 years as Chief Operating Officer, I am excited about this next chapter and the opportunities it brings to better meet the full end-to-end outsourcing needs of both our existing and potential new clients. We have created a single source provider of drug development, manufacturing, and packaging solutions focused on quality, reducing supply chain complexity, speed to market, and ultimately commercial success for our clients.

Q: How has the acquisition been received by your current clients?

A: Overall, general feedback from our clients has been very positive, with both LSNE and PCI clients having welcomed this latest development. We had already been supporting a number of the same clients prior to the acquisition and so for these clients; it was a very welcome move as it is seen as reducing supply chain complexity and risk. For LSNE, the acquisition brings all the benefits of being part of a larger, global organization and the opportunity to not only develop and broaden our sterile and lyophilization capabilities, but provide the additional resources to help our clients get their valuable drug products to patients faster.

With increased capabilities truly spanning the drug product lifecycle and with an integrated supply chain able to provide bespoke clinical and commercial packaging solutions, our clients can now leverage the benefits associated with working with a single supplier. They can rely on us to navigate risk, reduce complexity, and reveal the route to market. Several of our clients have already taken advantage of the much broader services we are now able to provide because of the benefits this delivers.

Q: What do you consider some of the key factors driving market trends in parenteral manufacturing?

A: Generally, one of the key drivers for growth in the parenteral drug market is the many advances with respect to biologic drugs, from monoclonal antibodies through mRNA products to oligonucleotides. The focus of many biopharmaceutical companies, regardless of size, has been the treatment of chronic disease states such as oncology and rare diseases. The complexity and relative stability of these drug products has heightened the need for parenteral delivery systems.

At the moment, the greatest factor fuelling the explosive rise in parenteral manufacturing is COVID-19 and the focus of the industry as it responded to the pandemic. When the pandemic first led to shutdowns, many biopharmaceutical companies struggled to find production space and had to expand their outsourcing network to meet the increased need for fill-finish manufacturing and cold chain capabilities. By taking a conservative approach in fighting the pandemic, we were able to support our clients remotely and did not shut down any of our facilities. This ensured we were there for our clients, providing the services needed to maintain product supply for their patients.

As a result, small and mid-size CDMOs began taking on projects larger CDMOs may have previously handled. This in turn forced some smaller organizations to implement new procedures and add new technology to increase cold chain capabilities for example. These CDMOs successfully emerged as key players in the pharmaceutical supply chain during the pandemic because they integrated new technologies and remained flexible in adjusting to the needs of their customers by maintaining constant communication with their clients, meaning they were able to meet their needs in what was a very dynamic market.

Additionally, distribution of vaccines and other therapeutics have highlighted the supply chain challenges of liquid formulations and the need of lyophilized products to support all geographic regions in need of these critical life-saving therapies. At PCI, we are experts in taking liquid formulations and developing robust lyophilized formulations with increased stability and less reliance on cold chain storage and distribution, which during the pandemic became critical. With our global distribution network, we ensure whatever the dosage format, our clients' valuable drug products reach the end-user in optimal condition whether that be a healthcare professional or patient.

Q: How are CDMOs and the industry adapting to the current manufacturing environment for parenterals?

A: CDMOs, including PCI, have had to adapt relatively quickly to meet the growing market requirements and ease the strain on the global supply chain. At PCI, for example, we have not only expanded our biologic packaging and cold chain storage and distribution capacities but through the acquisition of LSNE, we have broadened our capabilities, and now truly span the biologic lifecycle with an integrated global proposition meeting our clients' end-to-end outsourcing needs. Having packaging, labeling, and distribution centers of excellence geographically

located to support our aseptic fill-finish sites, it allows us to quickly and safely process our clients' products and minimize any logistical challenges.

By offering greater flexibility and adding new capabilities, CDMOs must be united internally from top to bottom to account for every service. From the leadership team to engineering, project management, supply chain, and business development, all functional groups within an organization must be aligned to the company's vision with continuous and open lines of communication. At PCI, we learned that maintaining cohesion within the organization was crucial to our manufacturing processes – especially as we've continued to enhance our sterile fill-finish and lyophilization capabilities, which will prove beneficial for long-term success.

Q: How are vaccine development and production needs impacting the industry?

A: With the unprecedented surge in the development and production of COVID-19 vaccines and therapeutics, there has been significant impact on material availability across the pharmaceutical supply chain. All CDMOs operating in the sterile fill-finish space typically use the same processing components: tubing, connectors, vials, stoppers, vessels, and filters, and we are all facing similar challenges concerning lead times. Currently, lead times vary significantly, with the purchase and receipt of filters, for example, taking up to 12 months or more, which obviously affects the client's clinical study or launch plan.

To ensure a continuous supply for our clients and to meet patient needs, we have successfully navigated such potential supply chain challenges. Utilizing PCI Bridge, our integrated and predictive supply chain management platform, we have worked with our clients, adjusting forecasts, ordering additional supplies, and leveraging existing relationships and partnerships to source materials as needed to ensure project milestones are met.

Q: What are the major challenges for parenteral drug product development and manufacturing?

A: Both biopharmaceutical companies and their CDMO counterparts, such as PCI, are facing increasing complexity across all aspects of the parenteral drug development and manufacturing supply chain. The move toward more targeted, specialty drugs and more complex molecules in patient-centric delivery systems means additional challenges in terms of formulation and analytical development, manufacturing, and packaging.

With the increasing focus on personalized medicine and treating orphan designated disease states, it means more niche products and smaller batch sizes with the same pressure on delivering speed to market. Ensuring a flexible, integrated approach to scalable development and manufacturing is vital in delivering these specialized products to the market in the most cost- and time-efficient way.

Q: How is PCI uniquely qualified to address those challenges?

A: With more than 25 years of experience in lyophilization and sterile fill-finish manufacturing and the specialized packaging of biologics, PCI has developed industry-leading technical expertise in the end-to-end processing of these often challenging and complex molecules. We truly support full product lifecycle management from formulation and lyophilization cycle development through clinical to commercial manufacturing, packaging, labeling, and distribution. With more than 90 new product launches every year, PCI is an extension of our customers' supply chain, trusted to deliver, each and every time.

Our experience with a wide variety of novel drug products paired with our flexible cleanroom space offers a solution to challenging complex formulation processes for emulsions, suspensions, liposomes, polymer nanoparticles, and Lipid Nanoparticles (LNPs). We pride ourselves on our flexibility, agility, and speed, allowing us to find creative solutions, driving development and connecting commercialization.

Our experienced and highly skilled team work closely with our clients to fully understand their complex formulations and project needs before developing unique programs, taking customized processes from the bench to GMP.

With personalized medicines, high-value bulk drug substances, and APIs, handling smaller batches while minimizing product loss is critically important. To address these challenges, PCI has invested in state-of-the-art robotic sterile fill-finish technology, delivering the highest standards of sterility by removing human intervention.

Meeting the demands of a dynamic marketplace, whether it be for sterile process development, scale up, technology transfer, or bespoke packaging of biologic drug products, PCI provides a collaborative, creative and tailored approach to deliver upon our mission of being the bridge between life-changing therapies and patients.

Q: What are the future plans of PCI for developing the sterile fill-finish service offering?

A: As part of our global strategy to increase our sterile fill-finish capabilities and to address the ongoing global capacity shortage, PCI is continuing to build upon its current capabilities to assist both existing and new clients in drug development and manufacturing. PCI has recently added an additional large-scale lyophilizer to our Madison, WI, facility, and we are expanding our presence in New England with a supplementary high-throughput commercial facility in Bedford, NH.

We have further invested in industry-leading robotic technology to complement our global sterile fill-finish capabilities. This investment comprises two robotic Cytiva Microcell Vial Filler units for clinical-scale manufacture, one located in San Diego, CA, and one in Melbourne, Australia. In addition, a larger-scale Cytiva SA25 Aseptic Filling Workstation is also located at our San Diego facility, allowing us to deliver a seamless, end-to-end, sterile fill-finish solution across multiple dosage forms and from small- to larger-scale production runs meeting the needs of our customers.

This advanced robotic technology expedites the filling process with state-of-the-art automation, and the gloveless isolator removes the need for human intervention to achieve the highest levels of sterility. In addition, the robotic accuracy avoids the closure activity failures typically experienced with more traditional filling techniques.

Through the acquisition of LSNE, the further investments planned to enhance our sterile fill-finish capacity and technologies, combined with our global packaging centers of excellence means PCI is a trusted and experienced partner able to deliver on our mission to deliver life-changing therapies to patients. ◆

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MEDICAL DEVICE UX DESIGN

Bridging the Divide Between People & Products: How UX Design Can Improve Medical Device Product Development

By: Aditya Jagannathan

INTRODUCTION

In the medtech industry, product development has traditionally followed a classic, top-down approach focused on the technology, and not the user.[1] Moreover, when it comes to developing medical devices for patients who self-administer their medication, engineers often believe the devices are "simple to use" and tend to overlook the emotional impact these patients experience and the lack of training they receive.[2]

Human factors and industrial design can bridge the divide between people and products to maximize the likelihood that new medical devices will be safe and effective for the intended uses, users, and use environments.

THE GROWING TREND OF MEDICAL DEVICE UX DESIGN

Medical device user experience (UX) design is emerging as one of the top trends in healthcare, driven by the rising expectations for medical devices that are simple to understand and operate. In addition, today's patients and healthcare professionals expect well-designed products that reduce anxiety, increase efficiency, and improve patient outcomes.

According to Dorothy Shamonsky, PhD, Chief UX Strategist at Integrated Computer Solutions Inc., the user experience should be the starting point of designing any product. And yet, it still happens all too often that when a product is designed by engineers, only when it is almost complete is the user experience considered; much too late to make any significant changes.[3]

From a user's perspective, UX design is important because it means they can effectively reap the benefits of the device. "There is less training time, more ease of use and satisfaction, optimal device use, fewer errors in use, they are safer, and there are better outcomes from device use," explains Shamonsky. "From the product owner's perspective, UX makes their product more effective with users and more saleable. This leads to better patient outcomes, preempts device complaints, reduces product liability, and facilitates the regulatory approval process."

The Role of Human Factors Engineering

Human factors, or people-centered, engineering (HFE) focuses on improving areas within a product or design where interaction happens. The goal is to reduce the incidence of use-errors and produce more comfortable interactions with a product. It's about understanding human capabilities and limitations, and then applying this knowledge to product design using a combination of many disciplines, such as sociology, engineering, and industrial design.[4]

In the medtech field, greater attention is being paid to

human factors and usability engineering, thanks to an FDA guidance issued in 2016 that considers them essential components of product development for combination products and medical devices. The US FDA guidance recommends making human factors and usability engineering a robust part of the design control process to maximize the likelihood that a new device will be safe and effective for its intended users and use environments.[5]

Usability deficiencies can result in a delay in patients receiving otherwise effective treatment, as well as lost time and revenue for the sponsoring company. In a competitive healthcare delivery environment, delays can also mean lost market share that is difficult to recover.

BRIDGING THE DIVIDE BETWEEN PEOPLE & PRODUCTS

More and more, biopharma companies and original equipment manufacturers (OEMs) are applying HFE principles across the entire lifecycle of bringing a new medical device to market in order to incorporate the user experience.

Human factors engineering provides evidence that a device and its labeling can be used safely and effectively by the intended user in the intended use environment. The process involves testing the numerous touchpoints where patients interface with a drug product, including packaging, Instructions for Use (IFUs), prescribing information, quick reference guides, and device indicators and controls.[6]

Applying HFE to Improve Medical Device Product Development

Noble is an Aptar Pharma company and industry leader in providing drug delivery training device programs for pharmaceutical companies and OEMs. Its Human Factors Plus (HF+) capabilities combine the application of human factors engineering with Noble's expertise in developing patient-centric training solutions and onboarding platforms to advance the development and testing of new self-administered medical products that optimize safety and efficacy while minimizing use errors and the risk of adverse events.

Ways to Incorporate UX Design Into the Product Development Process

Biopharma companies and OEMs are increasingly employing human factors and

usability engineering to incorporate UX design into product development. Noble supports this process all the way through regulatory approval and post-market analysis by directing its human factors capabilities to the following areas:

- Strategic planning for regulatory approval pathways
- Contextual inquiry – observation of users in their environments
- Formative and summative studies – iterating usability testing and applying learnings to improve or demonstrate the user interface
- Heuristic evaluations – HF expert review based on experience
- Task, IFU and training analyses
- Threshold analyses – systematic comparison to approved products
- Use-related risk analysis – hazards, severity, harm, mitigations
- Design of drug delivery and medical training devices and prototypes

SUMMARY

The benefits of human factors engineering and usability design range from a better understanding of patients' needs to producing easier-to-use devices and establishing more effective training; all of which lead to improving patient compliance and medical outcomes. Human factors engineering and UX design can also help reduce the risk of use errors, product complaints and recalls, and can de-risk the combination product regulatory approval process. These methods can be integrated into many touchpoints along the product development journey and produce tangible results that benefit patients. ◆

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BIOGRAPHY

Aditya "Adi" Jagannathan, with a decade of experience in developing combination products for leading pharmaceutical companies, is the Patient Services New Business Development Manager at Noble, an Aptar Pharma company and global leader in developing innovative patient-centric drug delivery training devices and onboarding solutions for the world's top pharmaceutical brands. He previously served as Clinical and Human Factors Program Leader for a global medical device company, where he led clinical product safety, efficacy and usability development for wearable drug delivery devices.

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AUTOMATION SOLUTIONS

The Future of Lab Tech Will Combine Automation, Accuracy & Agility

By: Rich Ellson and John Fuller, PhD

INTRODUCTION

COVID-19 has tested the scientific community. Challenges arose from vaccine design and development through increased testing to continuing research amid global supply shortages. As a result, researchers showed striking innovation and unprecedented agility. Times are changing, and we, in the life sciences, must be prepared and flexible. The pandemic shows the need to streamline and automate processes. It also warns us to be on guard for supply line failures. These processes speed the development of new medicines and vaccines.

Accelerating development comes down to designing and using flexible automation solutions. These solutions, along with smarter instruments and new consumable paradigms, help meet researchers' needs. Knowing how and when to use specific instruments and resources includes being strategic about the use of consumables, including plastic tips. Tip demand has increased during the pandemic as the supply of tips has been reduced by supply chain issues. For some workflows, plastic tips are non-negotiable. This is true when following standardized and regulated procedures or when microliter-to-milliliter volumes are involved. Recent tip shortages coupled with the fact that not all tips are equal (some available tips lack quality or compatibility with specific instruments) have led researchers to reconsider their liquid handling. Some workflows can leverage instruments with fixed tips — for example, workflows in which washing the tips is sufficient. In some cases, pairing liquid handlers with bulk fillers can reduce tip use if a reagent is common to all wells.

USING ACOUSTIC ENERGY TO MOVE LIQUIDS

Sometimes tipless solutions may be preferable, particularly for complex transfers or for miniaturization. One such instrument uses sound waves to move liquids. Focused acoustic energy from a transducer to the bottom of a source well of a microtiter plate causes a droplet of liquid to eject from the source well. The droplet travels a few centimeters and lands in the desired well of an inverted destination plate. This technique reduces the need for dilution plates, eliminates the need for tips, can reduce reagent usage by more than 90%, and can allow transfers to hundreds of thousands of wells per day.

To ensure the correct amount of energy is used and the focus is maintained, the system first audits each individual well to determine fluid depth and the basic nature of the fluid. This plate audit procedure uses low power acoustic pulses (similar to medical ultrasound) to disturb and record the effects of sound on the fluid. It takes only milliseconds per well. When a plate is audited, the acoustic transducer then addresses each individual source well with the energy needed to eject a droplet (with volumes as low as 2.5 nL). Droplets are ejected at 500 droplets per second to rapidly accommodate a range from nanoliter (nL) to microliter (μL). Liquid from any source well can be directed to any destination well. Different liquids in the source plate may be pooled into a single well of the destination. The entire audit and transfer process takes a few minutes and is compatible with wet and dry destination plates in 96-, 384-, and 1536-well formats.

One advantage of acoustic transfer in miniaturized experiments is the reduction of risk. Experimental errors due to solvent fluctuations and inaccuracies that can come from pipetting tiny

volumes go away. Researchers have found that compounds can stick to plastic. This may not matter for larger, 96-well assays, but when miniaturizing to 384- and 1536-well microplates, the math changes. The relative surface area of a tip increases compared to the volume the tip contains. This means that active components can be lost from the assay to the tip. In the end, and especially in miniaturization, it is the quantity of compound delivered rather than volume that is most important. Acoustic liquid handling tackles these concerns.

HOW IMPROVING ACCURACY CAN BOOST EFFICIENCY & LOWER COSTS

Part of the beauty of this marriage of automation and miniaturization is that it lowers costs for certain types of research by reducing the amount of materials and compounds required. Pharmaceutical companies were some of the first to integrate acoustic liquid handlers. In drug discovery, researchers test significant numbers of compounds on a given cell line or biochemical assay. These experiments are much less expensive in high-density microtiter plates. Using an acoustic liquid handler can be especially useful when testing combination drug therapy. As effective as combination drug therapy may be in reducing toxicity, the choices and ratios of drugs is difficult to study because one must determine joint efficacy across different doses of each compound. An acoustic liquid handler transfers any drugs, in any ratios, to any well. Synergistic potency shows up quickly and easily in the assay analysis.

Genetic engineering labs use acoustic liquid handlers in their efforts, largely to save time. Synthetic biology labs mix dozens of components in their experiments. This makes some of the most complicated workflows of any field. Acoustic liquid handlers can create droplets from dozens of different source wells, where the fluid properties of each well may vary, in rapid succession and pool them into a single destination well. Acoustic liquid handlers save researchers many hours in these assembly operations.

Yet, many situations and workflows need tip-based solutions, either alone or in combination with an acoustic liquid handler. Tip-based liquid handers are becoming extraordinarily advanced. They reduce the researcher's time commitment, both "hands-on time" pipetting as well as presence in the lab, while allowing customized solutions when research needs change. They allow automation of steps previously done by hand, including complex chemistry methods, as in next generation sequencing (NGS) library preparation, and even reagent identification and transfer.

Advanced instruments handle work-

"Accelerating development comes down to designing and using flexible automation solutions. These solutions, along with smarter instruments and new consumable paradigms, help meet researchers' needs. Knowing how and when to use specific instruments and resources includes being strategic about the use of consumables, including plastic tips."

flows that require a wide range of transfer volumes with air displacement pipetting with selective tip capabilities, along with sophisticated labware transport systems. Onboard technologies like advanced optics validate the accuracy of setup and allow the researcher load the deck and then leave the lab. The researcher can run and monitor the system remotely from desk or home. Importantly, highly automated liquid handlers often generate less hazardous waste, making them ecologically sound.

THE FUTURE OF ADVANCED AUTOMATION

Finally, other exciting instruments use other technologies to enhance automation. For instance, one automated instrument uses a magnetic mixer in the critical DNA cleanup needed for polymerase chain reaction (PCR). When paired with reagent kits incorporating magnetic bead technology, the instrument allows for a semi-automated cleanup process, reducing the number of touch points from 300 to 50, and reducing DNA cleanup time by half.[1]

These examples show how industry is using outside-the-box thinking to move toward greater automation, accuracy, and agility. Automated instruments make workflows easier, faster, and less costly. They allow the design of bespoke solutions to fit an organization's needs, even when those needs are evolving. Knowing when to use consumables and when to conserve them is important, as we look toward emerging from the supply crunch. Companies investing in future-facing technologies and solutions will continue to do so. These advances provide flexibility to move through uncertain times as we push into the next decade of research. As we continue toward greater sustainability, we will witness even more creative technologies and innovative instruments in the coming years. ◆

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BIOGRAPHIES

Rich Ellson is Chief Technology Officer and heads the Global Research Organization at Beckman Coulter Life Sciences. He joined the company in 2019 with its acquisition of Labcyte Inc., where he served as Chief Technology Officer, Board Director, and a Founder since 2000. He is the inventor of more than 80 granted US patents. Some awards of note include the 2006 PolyPops Foundation Award from the Society for Biomolecular Sciences (SBS) for acoustic dispensing technology and Northern California EY Entrepreneur of The Year 2013 for Life Sciences, and a Finalist in the National EY competition. In 2015, he was named a Technology Pioneer in 2015 by the World Economic Forum. He is a Fellow, prior Board member, and active volunteer in the Society for Laboratory Automation and Screening (SLAS).

Dr. John Fuller is the Global Commercial Product Manager for Echo Drug Discovery at Beckman Coulter Life Sciences. He was previously a field applications scientist for Labcyte. He earned his PhD from the U.N.T Health Science Center and completed a post-doctoral fellowship at Johns Hopkins University School of Medicine.

CDMO Services

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

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

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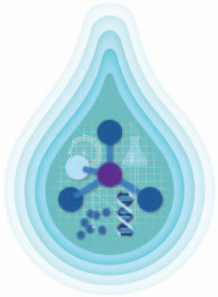

From its three early-phase drug development centers of excellence in Nottingham, UK, Somerset, NJ, and San Diego, CA, and its network of manufacturing facilities, **Catalent** offers its customers end-to-end solutions, encompassing early drug product formulation and dose form design, through to clinical supply services, commercial-scale manufacturing and lifecycle management. For early development, these solutions include analytical, pre-formulation and formulation technologies, and Catalent offers the most comprehensive bioavailability-enhancing technology toolkit including lipid formulation, spray drying, and hot melt extrusion. Its experience sees Catalent support the development and launch of over 150 new products every year. By adapting for each molecule's unique characteristics and challenges, Catalent uses its expertise and a wide range of tools and technologies to create dose forms that benefit patients. For more information, contact Catalent Pharma Solutions at (888) SOLUTION or visit **www.catalent.com**.

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

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DDL is an independent third-party, ISO 17025-accredited testing laboratory that provides package, medical device, and combination products testing. For nearly 30 years, DDL has provided extraordinary service and specialized testing expertise to the medical device and pharmaceutical industries. We employ a team of engineers, technical, and quality experts devoted to helping our customers bring medical device and combination products to market. Our single source, totally integrated approach enables organizations of all sizes from start-ups to globally recognized corporations maximize product performance, reliability, and safety while seamlessly achieving regulatory compliance. We work hard to build strong partnerships with our clients and have an unwavering commitment to assist in getting products to market on time. For more information, visit DDL at **www.DDLTesting.com**.

Formulation Technology

Enteris BioPharma is an independently operated and wholly owned subsidiary of SWK Holdings Corporation [NASDAQ: SWKH]. The organization's headquarters and 32,000- square-foot cGMP manufacturing facility is based within the heart of New Jersey's "Life Sciences Corridor." Through its pioneering and proprietary Peptelligence® technology, Enteris BioPharma partners with pharmaceutical and biotech organizations to develop bespoke solutions, including robust oral formulation development and clinical cGMP manufacturing. For more information, visit Enteris BioPharma at **www.enterisbiopharma.com.**

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

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

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As a world-leading drug delivery device solutions provider, **Nemera's** goal of putting patients first enables it to design and manufacture devices that maximize treatment efficacy. Nemera is a holistic partner and helps its customers succeed in the sprint to market with its combination products. From early device strategy to state-of-the-art manufacturing, Nemera is committed to the highest quality standards. Agile and open-minded, the company works with its customers as colleagues. Together, they go the extra mile to fulfil its mission. For more information, visit Nemera at **www.nemera.net**.

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Integrated Full Service Provider

PCI Pharma Services is an integrated full service provider, a proven and trusted partner to leading companies in the global healthcare industry. We offer unparalleled expertise and experience in taking compounds from the earliest stages of development through to successful commercialization, delivering speed-to-market and commercial success for our customers. Our core services support each stage of the product lifecycle, including drug development, clinical trial supply, commercial launch and ongoing commercial supply. We partner with clients in providing innovative technologies, flexible solutions, and an integrated supply network supporting lifesaving medicines destined to over 100 countries around the world. For more information, visit PCI Pharma Services at **www.pciservices.com.**

Global Data & Analytics

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

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Parenteral Delivery Solutions

Terumo Pharmaceutical Solutions develops patient-oriented parenteral delivery solutions for therapeutic performance and safety. Globally trusted for quality and precision, Terumo offers pharmaceutical and medical device manufacturers around the world comprehensive product design and development services as well as a portfolio of injection, infusion, and primary packaging solutions. Decades of experience collaborating with pharmaceutical companies from the earliest phases of drug development to the latest stages of product commercialization to optimize critical aspects of parenteral drug delivery. Our comprehensive parenteral delivery product portfolio of injection, infusion, and primary packaging solutions offer innovative drug delivery technologies ready for today's most demanding applications. For more information, visit Terumo Pharmaceutical Solutions at **www.terumopharmaceuticalsolutions.com.**

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Vetter is a leading contract development and manufacturing organization (CDMO) that specializes in the aseptic filling and packaging of syringes, cartridges, and vials. The company has extensive experience with biologics and other complex compounds. Collaborating with pharma/biotech clients worldwide, Vetter supports products from preclinical development through global market supply. Through its US and European facilities, Vetter Development Service provides state-of-the-art support for early stage products, with transfer at Phase III to Vetter Commercial Manufacturing for large-scale production. For more information, visit Vetter at **www.vetter-pharma.com.**

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