Drug Development & Delivery

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BILL HARTZEL

GATTEFOSSÉ

Drug Release Timing is Everything

Excipients for Modified Release

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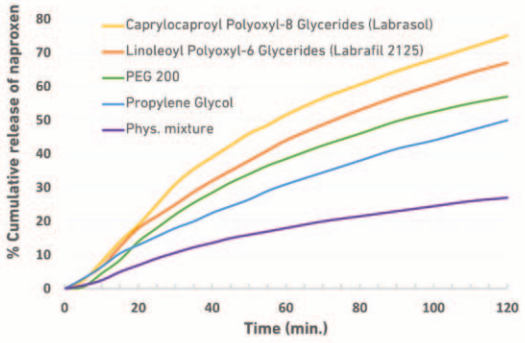
Naproxen loaded liquids adsorbed onto solids (2019 Lam)



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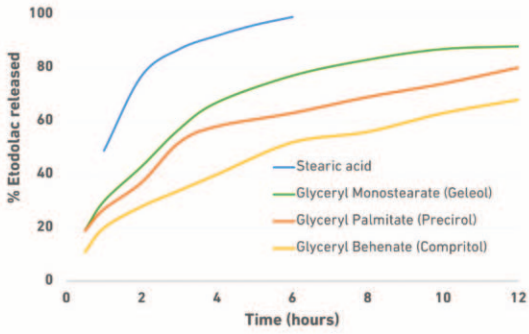

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- \+ In-vivo performance, efficacy
- \+ Biocompatibility, biosafety, biodegradability
- \+ Innovative & cost-effective development
- \+ Stable & safe drug products

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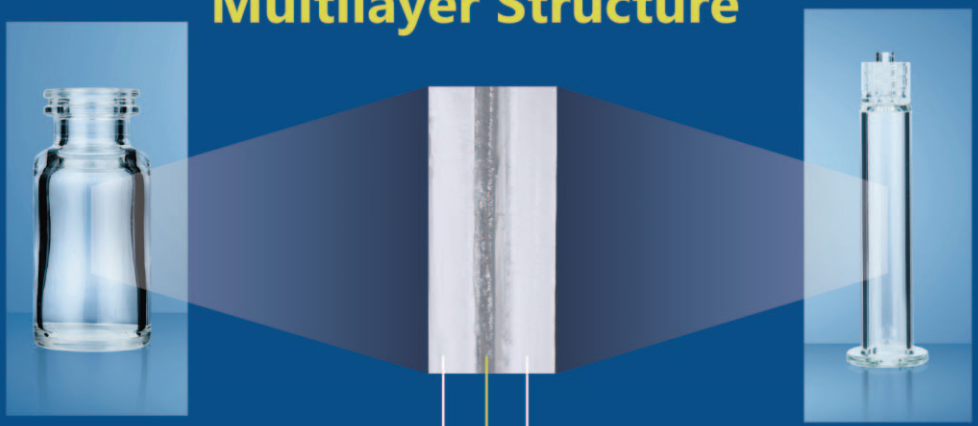
Multilayer Structure



Water Vapor Barrier Layer (COP)

Oxygen Barrier Layer (New Polymer)

Drug Contact Layer (COP)

- Excellent Oxygen Barrier
- High Water Vapor Barrier
- Very Low Extractables
- Low Protein Adsorption
- Excellent Ultraviolet Barrier
- High Break Resistance
- High pH Stability
- Silicone Oil Free Barrel
- Gamma-sterilized Vial & Syringe
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- For Biologics & Gene/Cell Therapy

2, 6, 10, 20mL Vial

Nest & Tub for Vial

1, 2.25mL Syringe

Nest & Tub for Syringe

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1952-2022 INTO THE FUTURE... WITH CONFIDENCE AND CONSCIENCE

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Injection Device Trends

"The development of combination medicines, biologics, and biosimilar compounds is on the rise. The successful use of these novel and life-saving drugs has become increasingly dependent on innovative and cost-effective delivery methods, such as autoinjectors, on-body injectors, and other devices that support patients' functional and lifestyle needs."

p.44

Departments

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Ranok Therapeutics Announces Initiation of Patient Dosing in a Phase 1/2 Clinical Trial of First-in-Class BRD4-Targeting CHAMP Protein Degrader

Ranok Therapeutics recently announced the initiation of patient dosing in the US for a Phase 1/2 study of RNK05047. The trial, entitled CHAMP-1, will evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of RNK05047 in patients with advanced solid tumors or diffuse large B-cell lymphoma (DLBCL). Ranok anticipates preliminary data from the study in the second half of 2023.

"RNK05047 is Ranok's first therapy based on our proprietary CHAMP technology, as well as the first BRD4 protein degrader in the pharmaceutical industry to enter clinical testing," said Weiwen Ying, PhD, Founder and Chief Executive Officer of Ranok. "RNK05047 is designed to selectively degrade BRD4 protein preferentially in tumors, thereby improving safety and efficacy, which differentiates it from other investigational therapies such as non-selective BET inhibitors."

"The BET bromodomain transcription factor BRD4 is a master regulator of oncogenes involved in diverse cancer types," added Manuel Hidalgo Medina, MD, PhD, Chief of the Division of Hematology and Medical Oncology at Weill Cornell Medicine and New York-Presbyterian/Weill Cornell Medical Center, Associate Director of Clinical Services at the Sandra and Edward Meyer Cancer Center at Weill Cornell Medicine and a site Principal Investigator in the trial. "We are pleased to be participating in this trial and are hopeful that RNK05047 will provide a beneficial new therapeutic option for patients."

Ranok's proprietary Chaperone-mediated Protein Degradation/Degrader (CHAMP) platform and Chaperone-Tether Library are based on our founders' extensive backgrounds researching protein homeostasis. CHAMP technology takes advantage of the cellular chaperone network, which regulates the folding and stability of proteins, distinguishing it from other targeted protein degradation approaches. CHAMP has a number of unique advantages, such as the evasion of mechanisms of drug resistance, and is designed to improved safety and efficacy due to the selective targeting of disease tissues.

RNK05047 is a first-in-class, small-molecule, tumor- and BRD4-selective protein degrader that was discovered and developed using Ranok's proprietary approach to targeted protein degradation, CHAMP. The bromodomain transcription factor BRD4 is a key regulator of oncogenes such as MYC and BCL2 and is involved in diverse cancer types. CHAMP-1 is a Phase 1/2 trial of RNK05047 currently underway in the US that will assess its safety, tolerability and pharmacokinetics, and also includes measures of anti-tumor activity and pharmacodynamic readouts as secondary endpoints. Preliminary data is expected from the trial in the second half of 2023.

Ranok is a privately held biopharmaceutical company that is pioneering CHAMP, an innovative approach to targeted protein degradation for the discovery and development of novel therapeutics. Our R&D team brings deep biological insight and chemistry expertise to rapidly identify and advance CHAMP degraders for a variety of important disease targets, with the goal to create transformative medicines that benefit patients around the world suffering from cancer and other serious diseases.

Zerion Pharma & Hovione Extend Partnership to Cover Use of Dispersome Technology Platform in Nutraceuticals

Hovione and Zerion Pharma A/S (Zerion) recently announced an extension of their collaboration on Zerion's Dispersome technology into the nutraceutical/dietary supplements field. Many dietary supplements suffer from low solubility. This results in poor bioavailability and consequently limits the physiological effect of the supplement. To overcome these limitations, the two companies will collaborate and apply the solubility-enhancing Dispersome technology for the development and commercialization of certain nutraceutical products.

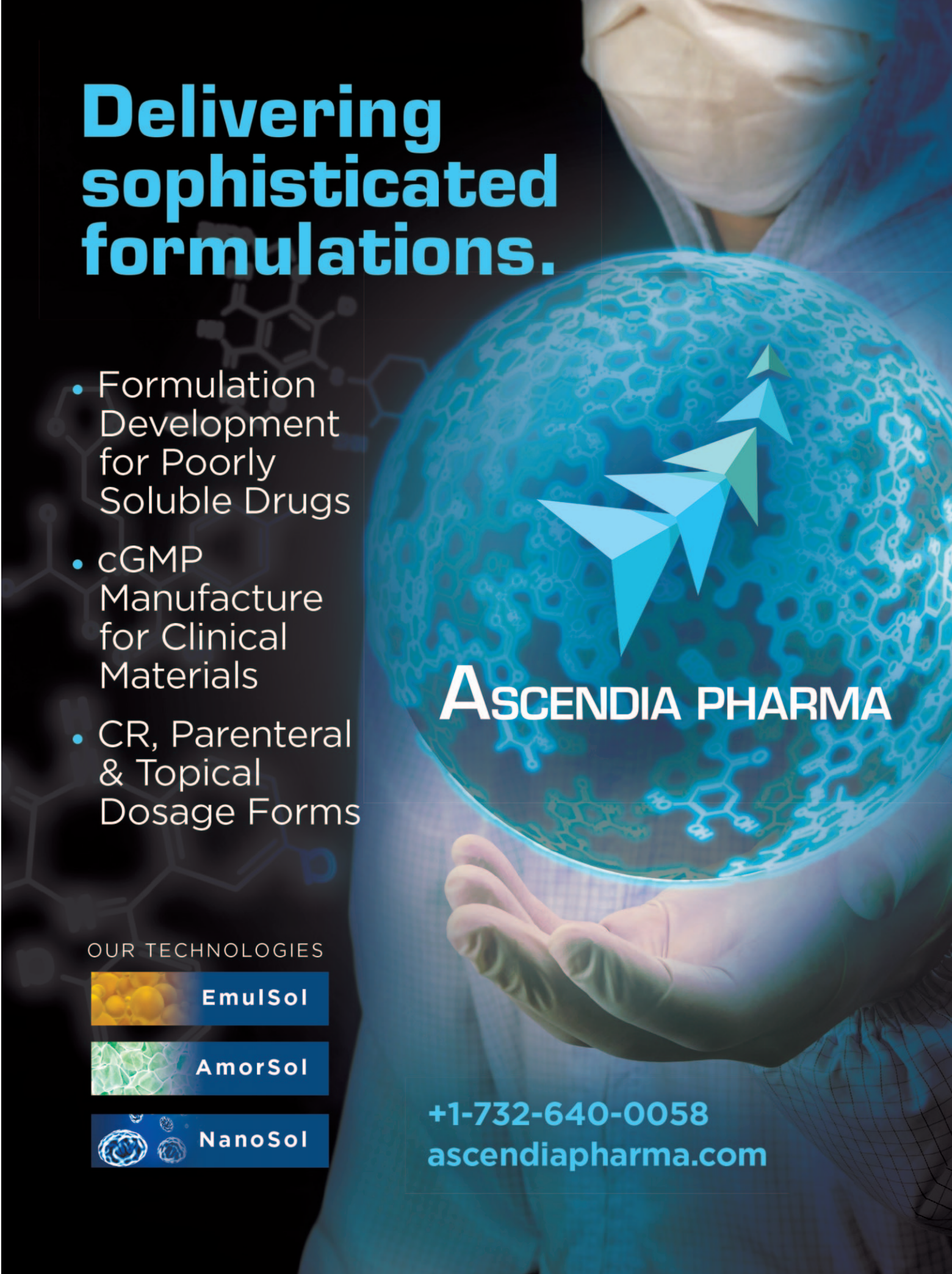
The first product candidate selected for joint development is an antioxidant with multiple health benefits and known for its extremely low solubility and bioavailability. By applying the Dispersome technology, Zerion has been able to demonstrate significant solubility improvements of this antioxidant. Under their collaboration, Hovione and Zerion will now upscale and develop commercial formulations of the antioxidant using the Dispersome platform and make these products available for distribution by partners globally. Under the terms of the collaboration agreement, the two companies will share income from the commercialization of these products according to their respective contributions.

In addition to the joint development projects, Zerion has granted Hovione an exclusive license to exploit the Dispersome technology for other nutraceuticals/dietary supplements. In return, Hovione will pay Zerion license fees and royalties on sales of the licensed products.

"The low oral bioavailability of some of the health-promoting nutraceutical compounds is a well-known challenge. The problem is compounded by the fact that some of the solutions used in pharma cannot be used in foods," said Jean-Luc Herbeaux, CEO of Hovione. "Hovione is thrilled to be Zerion's exclusive partner for the application of Dispersome to the fields of nutraceuticals and dietary supplements. The Dispersome platform and its enabling ingredient – beta-lactoglobulin or BLG – afford formulators new options which address unmet needs of the industry."

"I am extremely pleased with this extension of our collaboration," added Ole Wiborg, CEO of Zerion. "The Dispersome technology is actually very well suited for use in dietary supplements because it employs BLG as its solubility enabling component. BLG is a sustainable natural material and in itself a beneficial nutritional product that we source in high quality from Arla Food Ingredients. Since we as a company only have limited resources to exploit these promising applications of the Dispersome technology in the nutraceutical field, the collaboration with Hovione is a win/win situation."

In February 2022, Zerion and Hovione announced a strategic partnership aimed at commercializing the Dispersome technology within the drug development field. Under this partnership, Hovione and Zerion are offering pharma and biotech companies worldwide access to an innovative drug delivery platform combined with an unparalleled experience in formulation development, scale up, and GMP manufacturing. This unique combination provides customers in the pharma industry with a line of sight over the entire drug development life cycle from the preclinical phase to commercial drug product.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Oculis Announces Phase 2 Data Showing Topical Eye Drops Anti-TNFα Agent Licaminlimab Relieves Persistent Ocular Discomfort in Severe Dry Eye Disease

Oculis S.A. recently announced results of the double blinded, multicenter and placebo controlled Phase 2 clinical trial assessing the effect of topical licaminlimab (OCS-02) on global ocular discomfort in patients with severe dry eye disease (DED) (NCT02365519) has been published by the Clinical Ophthalmology journal. The publication is accessible on the National Institutes of Health (NIH) website here.

The results from the study show that the change from baseline to Day 29 in the global ocular discomfort score, the primary efficacy endpoint, was statistically significantly greater for topical ocular licaminlimab (OCS-02) (-7.9) than for vehicle (-3.6) (90% CI -7.7, -0.8; p = 0.041). The percentage of patients with an improvement in global ocular discomfort score >20 from baseline to treatment day 29, one of the main secondary efficacy endpoints, was statistically greater for licaminlimab (17.9%) compared to vehicle (4.7%) (p=0.018).

Licaminlimab (OCS-02) was well tolerated in this study, with no major safety differences between licaminlimab (OCS-02) and vehicle treatment groups, and no increase in intra-ocular pressure was observed.

Licaminlimab (OCS-02) is a single-chain antibody fragment (scFv) that binds to and neutralizes the activity of human TNFα, with dual mechanism of action (MoA), anti-inflammation and anti-necrosis. Unlike full-length monoclonal antibodies, scFv fragments can penetrate ocular surface tissues when used as eye drops, due to the smaller size of the molecule giving it the potential to become the first approved topical biologic for DED.

Dry Eye is a multifactorial disease in which inflammation rapidly takes on a central role in sustaining the pathological state. The global prevalence of DED has been reported at 11.59%, representing approximately 900 million people worldwide. In the US alone, there is currently between 16 million and 49 million people who have dry eye disease. Significant unmet medical needs remain for this large and growing patient population with only 9% of diagnosed patients in the US receiving treatment4 and despite current options, only 13% of patients are achieving lasting relief. Licaminlimab (OCS-02) is currently being investigated by Oculis in Phase 2 clinical trials for the treatment of dry eye disease and uveitis.

Oculis is a global biopharmaceutical company purposefully driven to save sight, improve eye care, and address significant unmet medical needs with breakthrough innovations. Oculis's highly differentiated pipeline includes candidates for topical retinal treatments, topical biologics, and disease modifying treatments. With a presence in key international markets, Oculis is poised to deliver life-changing treatments to patients worldwide. Headquartered in Lausanne, Switzerland and with operations in Europe, the US, and China, Oculis is led by an experienced management team with a successful track record and supported by leading international healthcare investors.

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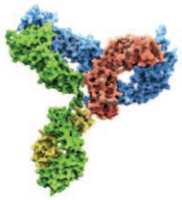
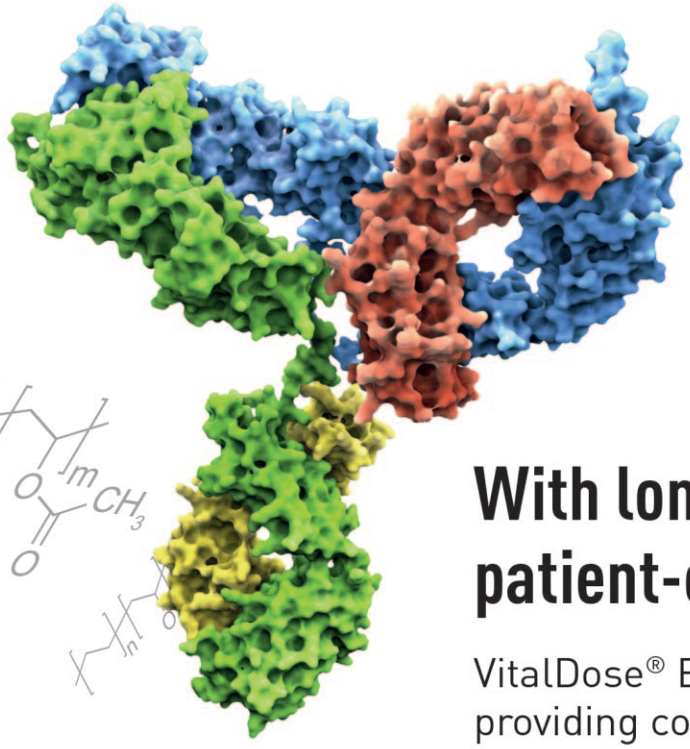
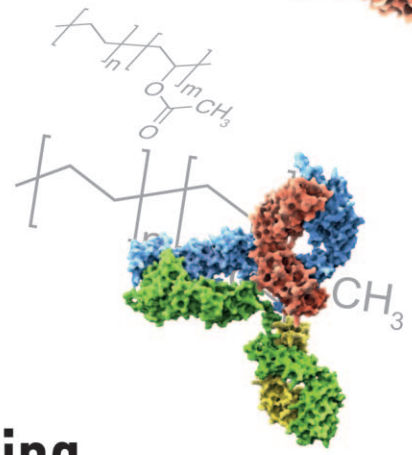
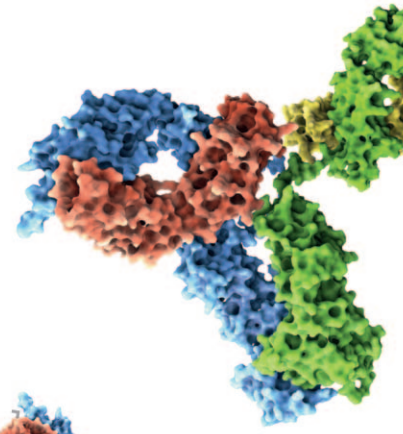


Sustained Drug Delivery







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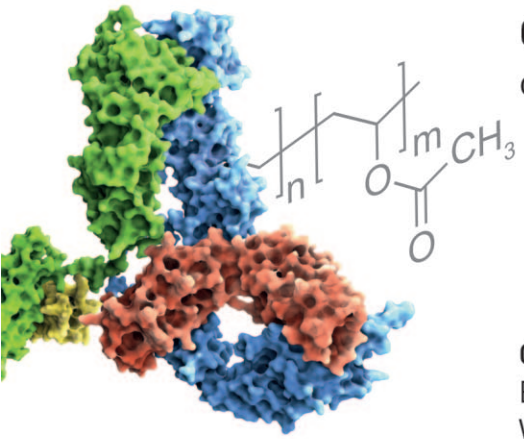

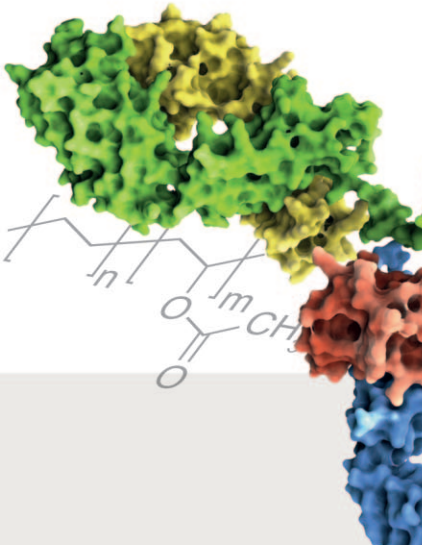

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Gerresheimer Invests Up to $94 Million in US Production Facility

Gerresheimer AG recently announced investments to rapidly expand its manufacturing, supply, and logistics capability for glass vials in the US. The project will be supported by the Biomedical Advanced Research and Development Authority (BARDA), part of the Office of the Assistant Secretary for Preparedness and Response (ASPR) at the US Department of Health and Human Services (HHS) with contracting support from the Department of Defense (DOD). It will expand Gerresheimer's capacity by new vial forming lines, including dimensional inspection, annealing, cosmetic inspection, and packaging. BARDA has agreed to provide up to approximately $66 million to Gerresheimer AG for this project. The investment is part of Gerresheimer's global expansion plan and follows its formula G strategy process.

Under the agreement, Gerresheimer will increase its annual production capacity in Morganton, NC, with interchangeable Type 1 vials (glass borosilicate and/or aluminosilicate) and Gx Elite Glass Vials capability. BARDA's financing, with contracting support from the DOD's Joint Program Executive Office for Chemical, Biological, Radiological and Nuclear Defense (JPEO-CBRND) and the Army Contracting Command (ACC), will strengthen the capabilities in the US to respond to current and future public health emergencies. The vials can be used in vaccination campaigns against infectious diseases, such as COVID-19 and others. This expansion of the facility will further strengthen Gerresheimer's leading market position in best-in-class elite vials.

"Gerresheimer is honored to support the US government in strengthening its pharmaceutical supply chain for current and future healthcare emergencies," said Dietmar Siemssen, CEO of Gerresheimer AG. "The agreement confirms our role as a supplier of system critical products, such as pharmaceutical primary packaging solutions and drug delivery systems for the healthcare sector. This investment follows our strategy process formula G and accelerates our growth in this important market."

As part of the project, the existing facility in North Carolina will be enlarged by the installation of new vial forming lines and a new warehouse. As the investment will lead to an increase in the number of people employed, new offices will also be part of the expansion plan.

The company is committed to sourcing the vast majority of its raw materials from US domestic suppliers in order to enhance the levels of responsiveness, dependability, quality, and domestic supply chain integration. Gerresheimer is furthermore incorporating sustainable design principles to implement energy efficiency measures, comply with storm water management requirements and reduce waste for the upgrades and expansion.

Gerresheimer is the global partner for pharmaceutics, biotech, healthcare, and cosmetics with a very broad product range for pharmaceutical and cosmetic packaging solutions and drug delivery systems. The company is an innovative solution provider from concept to delivery of the end product. Gerresheimer achieves its ambitious goals through a high level of innovative strength, industrial competence and concentration on quality and customer focus. In developing innovative and sustainable solutions, Gerresheimer relies on a comprehensive international network with numerous innovation and production centers in Europe, America, and Asia.

Saama Collaborates With Merck to Build Machine Learning-Powered Clinical Data Layer to Strengthen Clinical Development Capabilities

Saama Technologies, LLC recently announced a multi-year agreement with Merck, known as MSD outside the US and Canada, to build and operationalize a new clinical data layer leveraging Saama's Life Science Analytics Cloud (LSAC) to strengthen Merck's clinical development capabilities and expedite pipeline progress.

"Saama and Merck share a commitment to accelerating drug development and utilizing state-of-the-art Machine Learning for clinical data management processes. We are pleased to support the clinical development efforts of one of the top biopharmaceutical companies in the world," said Suresh Katta, Founder and Chairman Emeritus, Saama Technologies. "LSAC will enable Merck's team to optimize and automate processes, accelerate cycle times, and reduce costs in the quest to bring new treatments to patients sooner."

Under the agreement, Merck will integrate LSAC into its clinical development systems to improve speed and efficiency related to the ingestion, curation, and transformation of data and facilitate processing from multiple internal and external data sources to multiple business platforms and analytics needs.

"With the increasing demands of Merck's growing pipeline, it is crucial that we continue to embrace the latest digital technologies to optimize and expedite our data management, clinical trial operations and biostatistics capabilities," said Dr. Eliav Barr, Senior Vice President, Head of Global Clinical Development and Chief Medical Officer, Merck Research Laboratories. "By integrating Saama's Machine Learning-driven platform across our clinical functions we aim to fuel significant process efficiencies and elevate the user experience for our talented clinical teams."

"We are excited to strengthen our partnership with Merck and are committed to achieving transformational outcomes that expedite delivery of drugs to patients," added Vivek Sharma, CEO, Saama Technologies.

Saama's LSAC is an end-to-end, Machine Learning (ML)-enabled, clinical data management and cognitive insight platform designed to accelerate clinical research outcomes. The company's cloud-based, AI-powered solutions and services offer powerful data aggregation, monitoring, analytics, and collaboration capabilities, so sponsors and CROs can optimize drug development processes while ensuring the reduction of cycle times and data quality. In addition, technology-agnostic applications allow integration with existing systems. Saama's AI models are trained using more than a hundred million clinical data points and are easily embedded into existing infrastructure and business workflows.

Saama is the life science industry leader of ClinTech, the new category of purpose-built, AI-based clinical insights and automation platforms empowering faster, safer clinical development and regulatory programs. Over 50 biotech companies–including many top 20 pharmaceutical companies–use Saama's award-winning Life Science Analytics

Cloud (LSAC) platform to accelerate over 1,500 studies, including the clinical trial for the world's first COVID-19 vaccine. LSAC's rich applications facilitate unprecedented, authoritative oversight and automation of comprehensive clinical research data, enabling companies to file New Drug Applications (NDAs) more efficiently and bring treatments to patients sooner.

Catalent to Acquire Metrics Contract Services for $475 Million

Catalent, Inc. recently announced it has reached an agreement to acquire Metrics Contract Services (Metrics), a full-service specialty Contract Development and Manufacturing Organization (CDMO) with a facility in Greenville, NC, for $475 million from Mayne Pharma Group Limited. Upon completion, the acquisition will strengthen Catalent's capabilities in integrated oral solid formulation development, manufacturing, and packaging to help customers simplify and accelerate their programs, while also expanding Catalent's capacity to handle highly potent compounds.

The 333,000-sq-ft Greenville facility features comprehensive capabilities to accelerate and de-risk customer programs from early development through commercial launch through a streamlined one-site solution.

Over the past 5 years, the facility has seen more than $100 million in capital improvements and now includes 16 manufacturing suites, with 11 designed to handle highly potent compounds, as well as two packaging lines that can support a large variety of development and commercial supply programs. The facility's estimated annual production capacity exceeds 1 billion oral solid dose units.

"This acquisition will further expand Catalent's ability to meet our customers' expectations in fast-growing areas of the business and patient need. The experienced team and consistently improved, state-of-the-art facility in Greenville will provide Catalent's customers with immediate, fit-for-scale capacity for in-demand highly potent drugs and other oral solid small-to-mid-size batch needs. This capacity is particularly important for customers with R&D pipelines featuring accelerated, orphan, and rare disease programs for oncology and other important therapeutic areas," said Dr. Aris Gennadios, Group President of Catalent's Pharma & Consumer Health segment.

"Over the past several years, Metrics has undergone a period of transformational change to expand its footprint and service offering, becoming a global end-to-end novel oral solid CDMO. Catalent, a global leader in advanced drug development and manufacturing, is well-positioned to continue to invest in and accelerate the growth of Metrics and we believe this transaction will be extremely positive for our Greenville team and customers," added Scott Richards, Chief Executive Officer of Mayne Pharma.

The new facility will seamlessly integrate into Catalent's industry-leading oral development and manufacturing network, which includes flagship sites for large-scale and controlled release oral solids manufacturing in Winchester, KY, softgel development and manufacturing in St. Petersburg, FL, and additional facilities with bioavailability enhancement technologies and complex oral solids manufacturing platforms.

The acquisition is expected to close before the end of this calendar year, subject to customary closing conditions, and the entire team of over 400 employees will join Catalent. Mayne Pharma and Catalent have also agreed on the terms of a long-term supply agreement whereby the Greenville facility will continue to manufacture multiple Mayne Pharma products. Catalent will pay the purchase price for this all-cash acquisition using a combination of cash on hand, existing credit facilities, and, depending on market conditions, potentially new debt financing. The closing of the acquisition is not contingent on any financing activity.

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MindMed Announces First Patient Dosed in Phase 2b Trial of MM-120 in General Anxiety Disorder

Mind Medicine (MindMed) Inc. recently announced first patient dosing in its Phase 2b dose-optimization trial of MM-120, a pharmaceutically optimized form of lysergic acid diethylamide (LSD), for the treatment of Generalized Anxiety Disorder (GAD).

"The initiation of our Phase 2b clinical trial, the largest well-controlled clinical trial of LSD ever conducted, represents a major milestone for MindMed and for the many patients suffering from GAD," said Robert Barrow, Chief Executive Officer and Director of MindMed. "This exciting next step in the advancement of LSD builds on the positive topline data presented by our partners at University Hospital Basel in May 2022, which demonstrated the rapid, durable, and statistically significant effects of LSD and its potential to safely mitigate symptoms of anxiety and depression. The results of our Phase 2b trial will guide the dose selection and development strategy for our pivotal Phase 3 clinical trials, as we continue our efforts to bring a new potential treatment to the millions of people living with GAD."

The Phase 2b trial in patients diagnosed with GAD is a multicenter, parallel, randomized, double-blind, placebo-controlled, dose-optimization study. The trial plans to enroll 200 participants who will receive a single administration of up to 200 μg of MM-120 or placebo. The primary objective is to determine the reduction in anxiety symptoms 4 weeks after a single administration of MM-120, compared across the five treatment arms. Key secondary objectives, measured up to 12 weeks after the single administration, include assessments of safety and tolerability as well as quality of life. More information about the trial is available on our website (mindmed.co) or on clinicaltrials.gov (identifier NCT05407064).

GAD is a chronic, often debilitating mental health disorder that affects approximately 6% of US adults in their lifetimes. Symptoms of GAD include excessive anxiety and worry that persists for over six months, which can lead to significant impairments in social, occupational and other functioning, according to the National Institute of Mental Health (NIMH). While there is substantial diagnostic overlap between GAD, Major Depressive Disorder (MDD) and other major mental health disorders, there has been very little innovation focused on the treatment of GAD in the past several decades.

MindMed is a clinical stage biopharmaceutical company developing novel products to treat brain health disorders. Our mission is to be the global leader in the development and delivery of treatments that unlock new opportunities to improve patient outcomes. We are developing a pipeline of innovative drug candidates, with and without acute perceptual effects, targeting the serotonin, dopamine and acetylcholine systems. MindMed trades on NASDAQ under the symbol MNMD and on the Canadian NEO Exchange under the symbol MMED.

Daré Bioscience Announces Global Licensing Rights to Novel Antimicrobial Glycerol Monolaurate for Vaginal Health

Daré Bioscience, Inc. recently announced it has entered into a license agreement with Hennepin Life Sciences LLC under which Daré acquired the exclusive global rights to develop and commercialize treatments delivering the novel antimicrobial glycerol monolaurate (GML) intravaginally for a variety of vaginal health conditions, including bacterial, fungal, and viral infections.

GML is a naturally occurring fatty acid monoester that has shown broad antimicrobial activity, killing bacteria, fungi and viruses and importantly, represents a new class of antimicrobial agents. Additionally, due to its mechanism of action, GML has shown low potential for the development of antibiotic resistance. In vitro testing has shown GML to be effective at inhibiting growth of the major strains of Candida causing vulvovaginal candidiasis (VVC), as well as Gardnerella vaginalis, the primary bacteria associated with bacterial vaginosis. Furthermore, a randomized, double-blind pilot study investigating the effects of GML on vaginal microflora in colonized or infected women showed reductions in Candida and Gardnerella vaginalis while not altering the healthy Lactoacillus bacterium or vaginal pH.

"Vaginal health conditions, particularly infections such as bacterial vaginosis and VVC, which is second only to bacterial vaginosis as the reason women seek gynecological care, remain prevalent and serious problems that can negatively impact a woman's quality of life and create economic burden for women, employers, and the broader healthcare system. Women impacted by these conditions may have multiple episodes in a year, and treatments for one condition may increase the likelihood of developing another condition. We believe that an antimicrobial providing a broad spectrum of activity against bacteria and fungi, but with a low potential for developing resistance, represents a unique multi-target development candidate for our portfolio. GML could both delay recurrence following an effective primary treatment of an episode, as well as mitigate common side effects of the primary treatment," said Sabrina Martucci Johnson, President and CEO of Daré Bioscience. "As a company, we are committed to addressing unmet needs in women's health, including enhancing treatment options for vaginal health conditions. Earlier this year, Organon, a global women's healthcare company, and Daré entered into a global license agreement to commercialize Daré's XACIATO (clindamycin phosphate) vaginal gel, 2% for the treatment of bacterial vaginosis in female patients 12 years of age and older."

Under the agreement with Hennepin, Daré received an exclusive, worldwide, royalty-bearing license to research, develop and commercialize the licensed technology. Daré agreed to make potential future milestone payments through the term of the license based on clinical, regulatory, and commercial events, and to pay royalties based on commercial sales. Patents covering the licensed technology have been granted with terms through 2034 and additional patents pending would have terms through 2040.

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SOLUBILITY ENHANCEMENT

How Microparticles are Opening Doors to New Solutions for Oral Drug Delivery

By: Jessica Mueller-Albers, PhD, Yiming Ma, PhD, Alexander Bernhardt, and Michael Damm

INTRODUCTION

Solubility enhancement is still one of the main challenges in oral small molecule drug product development. A very high number of new chemical entities emerging from drug discovery is poorly soluble. Important therapeutic areas with poorly soluble new chemical entities include cancer, cardiovascular, infectious diseases, diabetes, and diseases affecting the central nervous system (CNS).[1] There are existing manufacturing technologies on the market to formulate poorly soluble drugs.[2] Amorphous solid dispersions (ASDs) are a very successful approach and show the strongest growth among all solubility-enhancing technologies.[3] ASDs are mainly produced using hot-melt extrusion or spray-drying processes that are well-established manufacturing techniques in the market.[4]

However, these processes cannot currently overcome all hurdles. Some Active Pharmaceutical Ingredients (APIs) are sensitive to high temperatures and high mechanical stress, and at the same time, have a low solubility in suitable organic solvents.[5] These limitations can lead to low spray solution concentrations. Moreover, poor particle engineering control in these processes results in cohesive powder with inferior flow properties, so that additional down-streaming steps are needed after the formation of the ASD.[6] However, this can stress the amorphous system and risk destabilization of the physical form. Also, handling of high potent APIs can be challenging using established manufacturing technologies.

Another important aspect to consider is final pharmacokinetic performance, which is not only dependent on the formulation, but can also be influenced by the manufacturing process.[7] Therefore, the orchestration of formulation and process development is key for success. In pharmaceutical drug product development, lab-scale processes often cannot be scaled-up seamlessly to commercial scale, creating risk of changing pharmacokinetic performance. In addition, the amount of API available from discovery is often insufficient to enter first-in-human studies with long process development steps. Therefore, a seamless transition from pre-clinical to clinical development is key for success.

Even though spray-dried dispersions, hot-melt extrusion, and solubilizing excipients are the most common techniques for solubility enhancement, the pharmaceutical sector needs further innovations to maximize the benefits of ASDs. The use of oral microparticles offers a potential solution.

The following focuses on the use of microparticles for solubility enhancement of oral small molecules and how this approach can address the challenges in pharmaceutical formulations.

MICROPARTICLES & THEIR SUCCESSFUL USE IN PHARMACEUTICAL FORMULATIONS

Microparticles, which consist of API and polymer, have been widely studied for decades as an attractive formulation technology for controlled and extended drug release. They are mostly developed as parenteral formulations. Following injection, microparticles continuously release the API and maintain the drug level within the therapeutic window over time to provide long-term therapeutic effects.[8] The API is encapsulated inside the poly-

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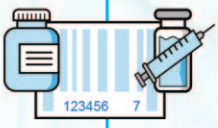

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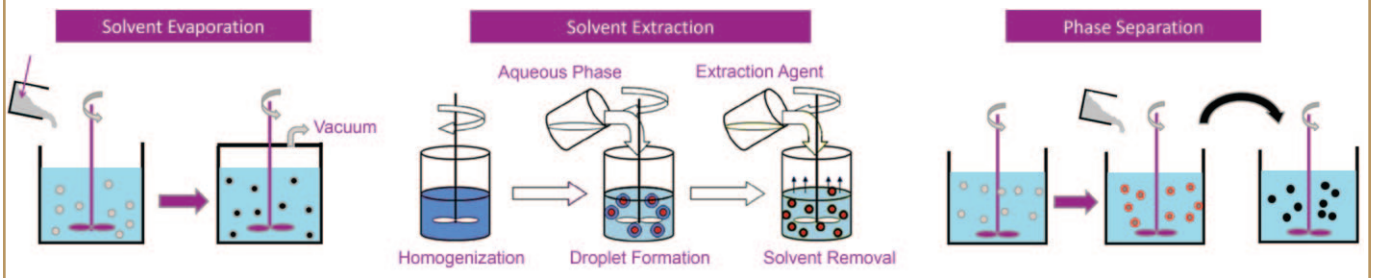
FIGURE 1



Different Types of Microparticle Encapsulation Technologies

mer matrix. Following administration, the polymer dissolves or degrades in the human body, then the API comes out from the microparticles.

There are several examples of commercial microparticle products, including for the alleviation of osteoarthritis pain and the palliative treatment of advanced prostate cancer. They usually come as a kit that includes the injection vehicle, the needle, and the microparticles. The microparticles are typically packaged in a vial or a prefilled syringe. They are re-suspended in the injection vehicle for administration. These products can have an extended release over different periods, for example, formulations for 1 or 2 weeks, 1 month, 3 months, or 6 months are available. The longest sustained-release product currently on the market is 10 months.

MICROPARTICLE ENCAPSULATION TECHNOLOGIES

There are three microencapsulation technologies used to make commercial microparticle products; solvent evaporation, solvent extraction, and phase separation.[9] Whichever technology used, it is important to understand the polymer properties. These play a vital role in creating the matrix structure of microparticles that affect the uptake of water, which then penetrates into microparticles, finds the API, dissolves the API, and then releases it.

The internal structure of microparticles varies depending upon the polymer and the API properties and the process conditions. In some cases, the API crystallizes during the microencapsulation process, particularly in products developed for extended release. In other cases, the API is just dispersed in the polymer matrix.

For solubility enhancement and ASDs, the APIs need to be molecularly dispersed in the microparticle matrix so that they have higher solubility for improved absorption.

Looking in more detail at a continuous solvent extraction process, API, polymer, and solvent are combined to form a dispersed phase, while surfactant is dissolved in water to form a continuous phase. There are several factors that have to be considered when preparing the dispersed phase, ie, the solubility of the polymer in the organic solvent and whether the API is dissolved or just suspended in the polymer solution.

Other factors affecting microparticle preparation include the preparation method for a single or a double emulsion, and how the chemical stability of the API in the dispersed phase is maintained.

The next stage is to take the dispersed phase and the continuous phase through the emulsion generator in which the emulsion droplets are formed. As soon as the emulsion droplets emerge out of the emulsion generator, the solvent is extracted out of the emulsion droplets.

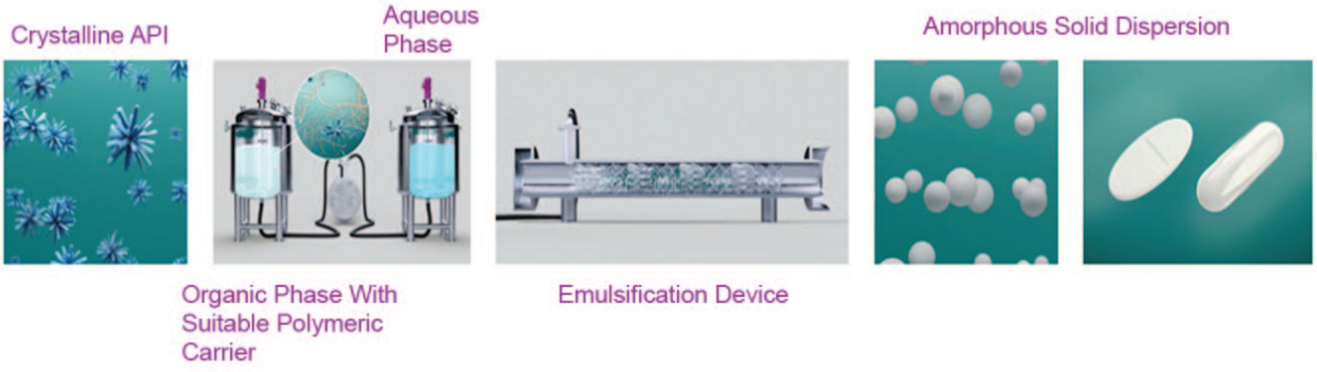
There are different types of emulsion generators available for making microparticles, such as static mixer, rotor stator, and Evonik-patented emulsion generators. Once the flow in the equipment has started, the dispersed phase is mixed with the continuous phase, and emulsion droplets are formed. By using different emulsion generators and different process conditions, microparticles of all different sizes can be prepared. It is possible to create microparticles from 20 μm to 50 μm, which is very attractive for injectables. In addition, microparticles below 10 μm for uptake by macrophages and above 100 μm for oral applications can be realized. Depending upon the application, the target microparticle size range can be adjusted.

SUCCESSFUL SCALE-UP

A vital part of any drug development is the move from the laboratory to commercial-scale manufacturing. The major tasks include scale-up of the process, production according to good manufacturing practices (GMP), as well as the regulatory evaluation of the process.

At early stages, only small batches of several grams are required; the process

FIGURE 2



Microparticle Process for the Formation of Ready-to-Fill ASDs

can be run in the fume hood, and several steps of the process can be run manually. This provides the flexibility to try different process concepts and troubleshoot very quickly.

When the project is moved to a later stage of development, such as clinical and commercial manufacturing, the batch size is at kilogram scale, and GMP production needs to be carried out to maximize the product safety and quality. The process also requires automated manufacturing and online controls that ensure high quality over the whole process. For scale-up in a continuous process, the tubing and equipment size can be increased to increase the flow rate of disperses. This continues proportionally so that the time for making a batch stays substantially the same as the process is scaled-up. Timing affects the properties of microparticles so this is important.

If the unit operation is longer, the properties of the polymers, the API, or the microparticles may change over time when the process is run. It is very important to keep good control on the process flow, eg, if longer unit operations have to be used or longer time processing, the time change can have an effect on the properties of microparticles. It is important to consider the product's recovery to make sure you have an efficient production process for manufacturing.

MICROPARTICLE TECHNOLOGY FOR ORAL SOLUBILITY ENHANCEMENT

The microparticle process was used to leverage the several advantages of the process to produce ASDs for solubility enhancement. Those advantages comprise the creation of uniform particle-engineered particles with a controlled target particle size at high yield, the free flowability of the resulting ASDs, as well as a seamless transition from pre-selection to clinical and commercial through mathematical modelling.

For this process, the crystalline poorly soluble API is dissolved with a polymeric carrier in a suitable organic solvent. At the same time, an aqueous phase is prepared. Both liquids are pumped into an emulsification device to produce perfectly round emulsion particles. After drying, this creates a free-flowing, ready-to-fill product.

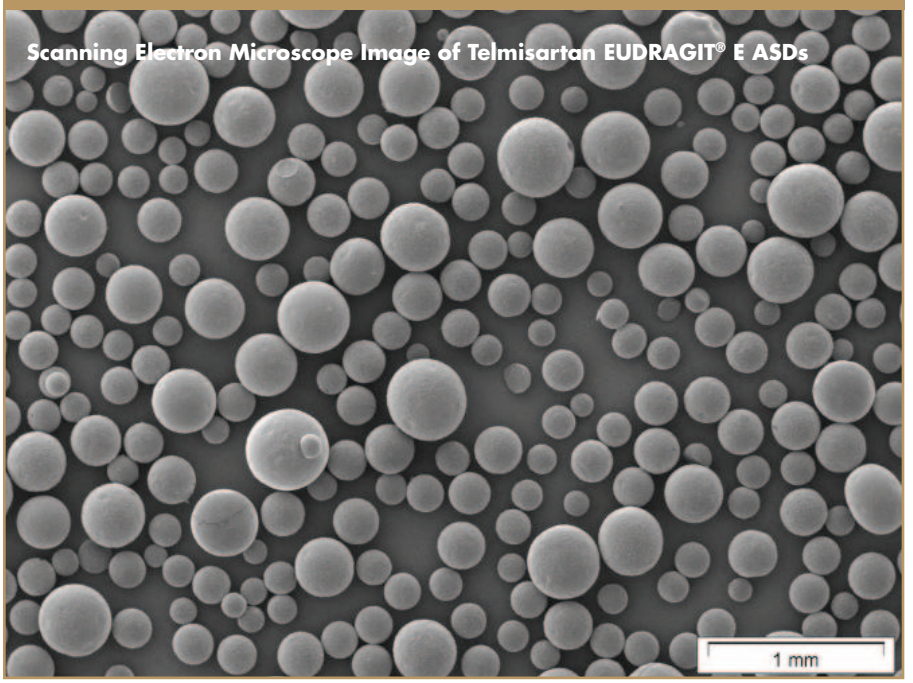
CASE STUDIES

The performance of the new oral microparticle process technology has already been proven with several poorly soluble drugs.

Telmisartan

Telmisartan is a cardiovascular drug with a high melting point of 269°C.[10] It is practically insoluble in water and is administered with a daily dose of 20 to 80 mg. EUDRAGIT® E PO was selected as polymeric carrier and processed together with telmisartan using the new process technology to create uniform round microparticles of size 200 μm (d50). Telmisartan remained in an amorphous state determined via XRPD after processing and 3 months stability at 25°C/60%rh and 30°C/65%rh. Dissolution was measured in a USP apparatus II at 150 rpm in 500-ml acetate buffer 4.0 for 2 hours. Pure telmisartan showed no solubility, and the oral microparticles increased the dissolution rate up to 80% in comparison to the crystalline drug. The results show that dissolution could not only be increased decisively with the new process compared to the pure crystalline drug after processing, but also was stable after 3 months storage at

FIGURE 3



25°C/60%rh and 30°C/65%rh (data not shown).

Bexaroten

Bexaroten is a cancer drug with a high melting point of 230°C. It is practically insoluble in water and administered with a daily dose of 75 mg. EUDRAGIT® E PO was selected as polymeric carrier, EUDRAGIT® RL PO was added to increase the Tg of the polymeric system and thus, physically stabilize the resulting microparticles. Bexaroten and both polymers were processed using the new process technology to create uniform round microparticles of size 163 μm (d50). Bexaroten remained in an amorphous state determined via XRPD. Dissolution was measured in a USP apparatus II at 150 rpm in 700 ml HCl for 15 mins followed by buffer pH 6.8 up to 3 hours. The results show that dissolution could be increased decisively with the new process compared to the pure crystalline drug and also compared to a marketed soft gel capsule. It is known from literature that ASDs tend to show stronger solubility enhancement than soft gel formulations, which was also visible in this case.

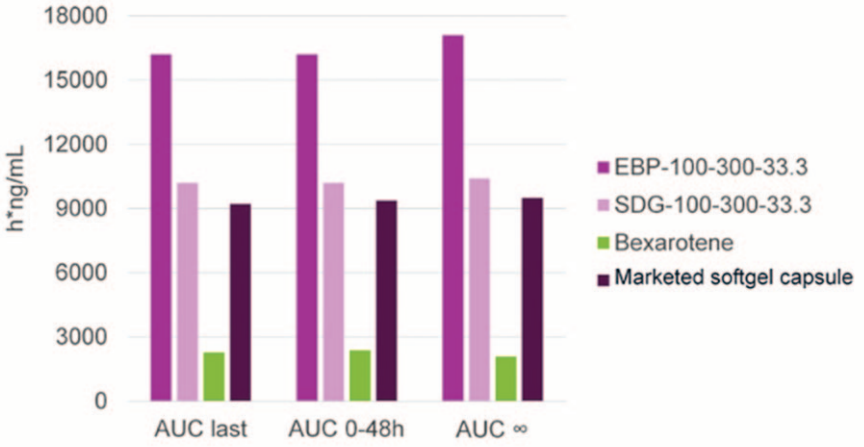
To investigate the more relevant performance comparison between an ASD prepared by the new microparticle process and spray drying, spray-dried dispersions with exactly the same formulation were prepared in house. For this purpose, the emulsion-based microparticles, the spray-dried dispersions, the crystalline API, and the marketed soft gel capsule were further investigated in an in-vivo study with beagle dogs. The bexarotene pharmacokinetic parameters in male beagle dog plasma following single oral administration showed a superior pharmacokinetic performance of the ASD prepared via the new microparticle process.

In summary, microparticles are a very beneficial process technology to create ASDs and thus, overcome solubility issues of small molecules for oral application. The microparticle process that is well-known from marketed parenteral drug products could be successfully transferred to an oral application and employed to manufacture stable ASDs using APIs with high melting points and poor aqueous solubility. With this new process, pharmacokinetic performance could be improved compared to standard processes known in the market.

CONCLUSION

Microparticles offer a potential extra avenue for successful solubility enhancement. However, when developing microparticles, it is crucial to understand and control the critical material attributes and the critical process parameters because they play an important role in establishing

FIGURE 4



Summary of Bexarotene Pharmacokinetic Parameters in Male Beagle Dog Plasma Following Single Oral Administration

microparticle properties. Formulation and process expertise is important for designing a microparticle formulation, scaling up, and commercialization.

We have illustrated that oral microparticles offer a unique solution to solubility enhancement when it comes to the formulation of challenging APIs, overcoming processing hurdles and optimizing pharmacokinetic performance. The new process facilitates the solubilization of highly challenging compounds, creates free-flowing powder through lean process with advanced particle-engineering control, and leverages the full therapeutic potential of an API. Finally, a seamless transition from pre-clinical formulation development to commercial manufacturing is key for fast first-in-human trials and successful final drug product development. ◆

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BIOGRAPHIES

Dr. Jessica Mueller-Albers joined Evonik's Health Care business line in 2010 and is currently working as Strategic Marketing Director for oral drug delivery solutions. Before taking over her current position, she was Group Leader for Drug Delivery, focusing on the development and analytics of new oral and parenteral platform technologies for the pharma and food industry as well as the development of cell culture media. She has held different positions in application service and formulation development of oral dosage forms and worked for a contract manufacturer, where she gained experience in developing solid and semi-solid dosage forms, product transfer, manufacturing of clinical-trial medication, GMP, and high potent handling. She earned her degree in Pharmacy from the University of Halle/Saale and her PhD from the University of Duesseldorf, where she specialized on melt extrusion of poorly soluble drugs. She is the author of several research papers, book chapters, and patents.

Dr. Yiming Ma joined Evonik's Health Care business line in 2018 and is currently Senior R&D Scientist at Evonik's Birmingham Laboratories, focusing on parenteral complex formulation development. Prior to joining Evonik, she was a Group Leader at WuXi AppTec for preformulation and developability assessment to support new drug development. She has extensive formulation, analytical, and process experience in the pharmaceutical industry with a focus on complex formulation development, such as microparticles and nanoparticles. She earned her PhD in Pharmaceutical Science and Nanotechnology from the University of Queensland, Australia, where she specialized in the development of targeted drug delivery systems based on microparticles and nanoparticles for cancer treatment. She has authored several publications in top tier pharmaceutical journals.

Alexander Bernhardt joined Evonik's Health Care business line in 2017 and is currently working as Head of the Drug Delivery & Applications group in the R&D department in Germany. He is an expert in the development of parenteral and oral drug delivery technologies and has extensive experience in the management of innovation and customer projects. He earned his degree in Pharmacy from the University of Regensburg, Germany, and gained experience in the field of drug nanosuspensions of poorly water-soluble drugs during his PhD at the University of Muenster, Germany.

Michael Damm is an Innovation Project Manager at Evonik, focusing on chemical technology. He began working at the company in 1992 and has expertise in process technology, particle engineering, as well as solubility and bioavailability enhancement of BCS II to IV drugs. He has built up a wealth of knowledge on the development of parenteral, inhalative, and oral drug products.

GENERATIVE AI TECHNOLOGY

Generative Machine Learning Can Construct Smooth Chemical Search Spaces for Efficient Drug Discovery

By: Jason Rolfe, PhD, and Ali Saberali, PhD, and Mehran Khodabandeh, MSc

INTRODUCTION

The fundamental steps of rational drug design include the identification of a clinically relevant target protein, the discovery of "hit" ligands that weakly modulate the target protein in the desired manner, and the optimization of selected hits for high potency against the target, low potency against all related off-targets, and good absorption, distribution, metabolism, excretion, and toxicity (ADMET). Target identification and the optimization of selected hits are informed by biology and medicinal chemistry, respectively. In contrast, the initial discovery of hits that are active against the target, and can be effectively optimized, is more dependent on exhaustive searching and luck. Conventional approaches for hit discovery are expensive, inaccurate, and can only explore a minuscule fraction of the full space of synthesizable, drug-like molecules.

Generative machine learning (ML) promises to efficiently optimize more accurate estimates of binding affinity and other pharmacological properties over the entirety of drug-like chemical space. Rather than exhaustively testing a screening library or making small changes to the best known compounds, generative ML maps chemical space to a smooth search space in which small moves correspond to small changes in potency, ADMET, etc. Within this search space, a diverse set of potent, selective, lead-like, and novel hits can be found efficiently. These hits can be drawn from the full extent of make-on-demand compound libraries comprising tens of billions of molecules, or even from de novo synthetic space. Hits can be jointly optimized for many properties simultaneously, making subsequent lead optimization easier, faster, and less expensive.

THE LIMITS OF (VIRTUAL) HIGH THROUGHPUT SCREENING

Drug hunters often identify novel initial hits by testing large libraries of compounds, either experimentally via high throughput screening (HTS); or computationally via virtual high throughput screening (VHTS).[1] HTS is expensive, and costs increase in proportion to the size of the screening library. While tens of billions of compounds are available for purchase, HTS is generally limited to between thousands and millions of compounds. VHTS expands the fraction of chemical space searched while minimizing experimental costs by computationally predicting binding affinity on a fixed library of drug-like molecules, and selecting only a small fraction with desirable predicted properties for further wet lab investigation.

VHTS may be performed using a ligand-based or structure-based pharmacophore. Such pharmacophores comprise significant ligand-protein interactions (hydrogen bonds, ionic, hydrophobic, etc) that are predicted to be consistent amongst strong binders (yielding a ligand-based pharmacophore) or are predicted to be consistent with the protein target (producing a structure-based pharmacophore). A chemical library can then be screened for compounds with low-energy conformers that match these pharmacophoric interactions, while avoiding obvious steric

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clashes with the target protein. Pharmacophores sidestep any mechanistic simulation of the dynamics of ligand-protein binding, maximizing computational efficiency, but their disregard for the physics of binding sharply limits their ability to generalize.

Binding affinity for VHTS may also be predicted using molecular docking, which uses the 3D structure of the target protein and knowledge of ligand-protein interactions to infer favorable binding modes of the ligand via a semi-heuristic minimization of the free energy. The resulting estimate more accurately captures the physics of binding than a pharmacophore model. Nevertheless, the free energy of binding is strongly affected by reorganization of the network of water molecules surrounding the ligand and protein, the deformation of the target protein induced by the binding of the ligand, and the loss of configurational entropy upon binding. These phenomena are difficult to capture accurately without a series of explicit solvent molecular dynamics (MD) simulations of every atom over time, requiring overwhelming computation.

Novel chemistries must be explored to discover new classes of compounds with superior properties, and to avoid existing patents. Fortunately, the chemical space available for drug discovery is astronomically large. Commercial make-on-demand libraries include tens of billions of compounds, and are growing at an exponential rate. De novo synthesis can easily access many orders of magnitude more compounds, and the full space of drug-like molecules is estimated to be between 1020 and 1060.[2,3]

On the other hand, the cost of HTS and VHTS scale linearly with library size. Even molecular docking cannot be run exhaustively on increasingly large make-on-demand libraries, let alone the full space of synthetically accessible, drug-like molecules. Alternative approaches to efficiently optimize over large chemical spaces, based upon more accurate estimates of experimental binding affinity and other molecular properties, are required to leverage progress in synthetic techniques for hit discovery.

DEEP LEARNING PROMISES TO IMPROVE MOLECULAR PROPERTY PREDICTION

Rather than explicitly modeling the ligand-protein binding process from first principles, it is possible to take a data-driven approach. Ligand- and structure-based pharmacophores are a simple example of this in which the activity of a query ligand is predicted based upon overlap with the pharmacophore of known actives. Quantitative structure-activity relationship (QSAR) models utilize data more flexibly, by applying simple machine learning (ML) techniques (typically decision trees, support vector machines, or neural networks) to features such as physicochemical properties or molecular fragments, to predict experimental activity.[4]

In general, these data-driven techniques define a rule that separates actives from inactives based upon a set of trainable parameters. For a ligand-based pharmacophore, the rule may be a threshold for the intersection-over-union of the pharmacophoric features of the query ligand versus the target pharmacophore. QSAR models may divide actives from inactives using a hyperplane in the space defined by the input features (linear models), a hyperplane in a space defined by nonlinear transformations of the input features (support vector machine or neural network), or a succession of thresholds on individual input features (decision trees).

Since around 2009, a deep learning revolution has transformed ML.[5] Whereas conventional machine learning algorithms used networks with one or two sequential layers of processing on carefully engineered features, deep learning algorithms have grown to thousands of sequential layers, hundreds of billions of parameters, and learn their own input features directly from the data. Such powerful deep learning models, with more complicated rules separating actives from inactives, promise to support more accurate activity prediction. However, they must generalize far beyond the experimental data used to train the models.

The cheminformatics community generally believes QSAR models can interpolate between data points, but not extrapolate outside of the available data, and thus cannot be used to perform VHTS over large, diverse libraries. Considerable effort has been devoted to characterizing the applicability domains of QSAR models based upon structural or physicochemical fingerprints, within which models are expected to interpolate accurately.[6]

In contrast, deep learning algorithms extrapolate accurately in domains like images, text, and speech. Small, semantically irrelevant changes in images, including shifts, scales, and rotations, induce enormous changes in the set of pixels that define an image. As shown in Figure 1, the pixel-based representations of images that depict the same class of object (eg, a cat) are almost as far from each other as they are from images that depict different object classes (eg, dogs, cars, houses). As a result, image classification in pixel space

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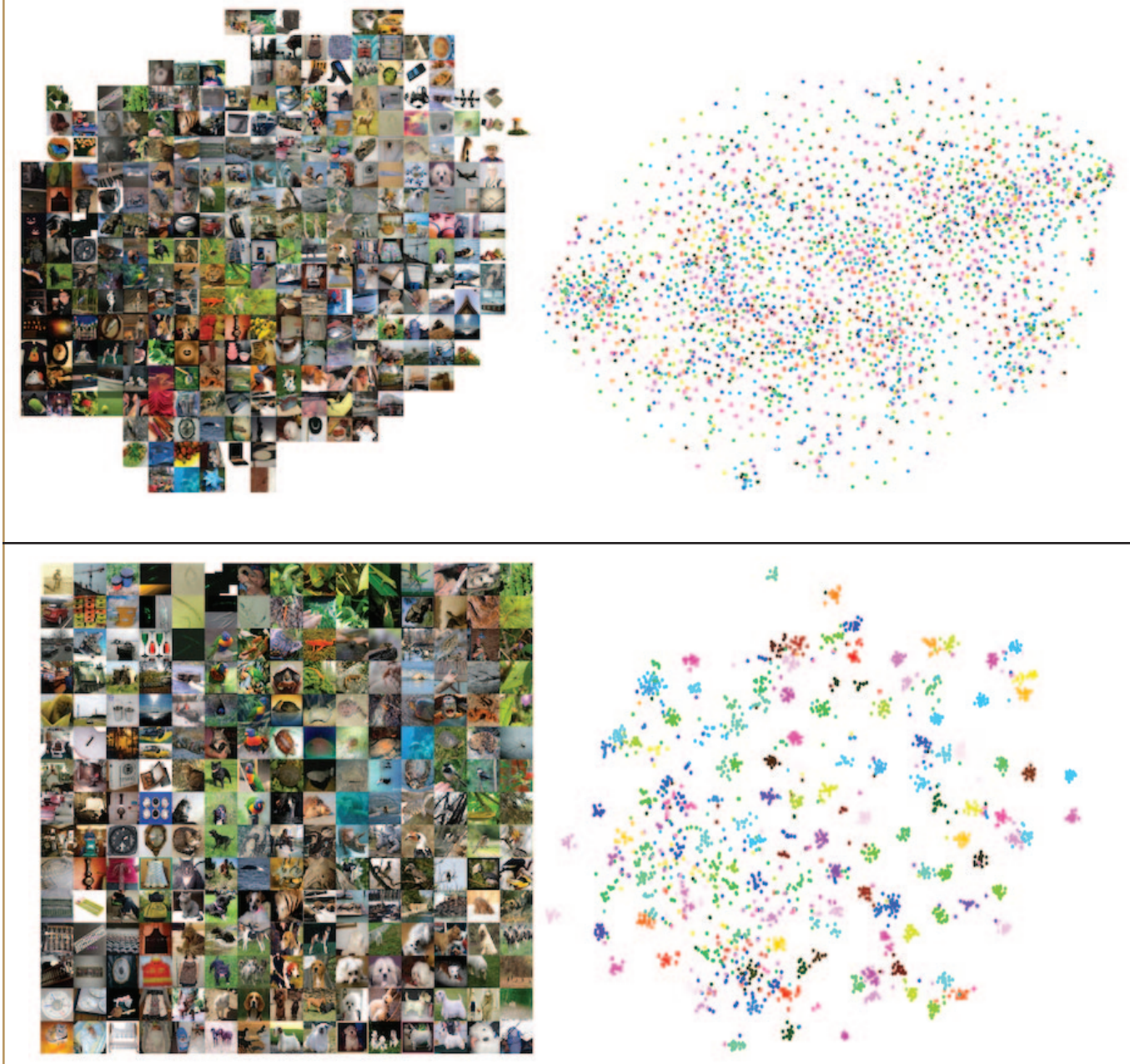
requires extrapolation from distant data points of the same class, rather than interpolation from nearby data points from different classes.

Deep learning algorithms nevertheless achieve excellent classification performance when trained on datasets comparable in size to those available for drug discovery. The most popular image dataset for machine learning is probably ImageNet, which has ~1,000 "actives" for each of 1,000 classes. State-of-the-art deep learning algorithms predict the correct class, out of 1,000 possibilities, on over 88% of test images; comparable to the 95% accuracy achieved by humans.[7,8] This exceptional performance is only possible because deep learning algorithms construct a representation that is smooth with respect to image semantics, rather than pixels, as shown in Figure 1.

The size of ImageNet is analogous to BindingDB, which has over 1M activity data points on over 500k ligands and

FIGURES 1A&1B



2D embedding (t-SNE) of images (left) and their labels (right) based upon their pixel representation (A) and representations constructed by a deep learning algorithm (B). In the native pixel representation, nearest neighbors are rarely of the same class, and extrapolation is difficult. The deep learning representation naturally organizes images by class, and extrapolation is easy.

thousands of protein targets.[9] Carefully designed deep learning algorithms thus promise to significantly improve the accuracy of molecular property prediction and optimization. To realize their full potential, such algorithms must complement the structure of the input just as image recognition algorithms embody the invariance of image content to small shifts, and address the noise endemic to pharmacological datasets.

Recently, ML has achieved notable successes in domains closely related to drug discovery. AlphaFold uses ML to predict the 3D structure of a protein based upon sequence and structure information from a large database of homologous proteins.[10] Fragments of 3D structure from similar proteins are nonlinearly stitched together, with residue sequences that exhibit complementary mutations across many homologous proteins encouraged to remain bound together. AlphaFold's output corresponds to a holo structure. It does not capture the change in protein conformation induced by a particular small molecule, and cannot be used directly to predict ligand-protein interactions. Nevertheless, complementary applications of ML promise to infer the relationship between structure and properties of small-molecule ligands.

GENERATIVE ML SEARCHES EFFICIENTLY OVER CHEMICAL SPACE

Small changes in molecular structure can induce large changes in molecular properties. This phenomenon, particularly evident across activity cliffs, makes optimization difficult and inefficient.[11] The sort of hill climbing performed by medicinal chemists during lead optimization, in which small modifications of the current best molecule are evaluated experimentally and the best modification is used as the basis for the next round of optimization, will generally get stuck in a bad local optimum. These local optima are like foothills surrounding a large mountain. A path that goes directly uphill from a random starting point usually gets trapped in one of these foothills. There is no sequence of small, beneficial modifications from such a bad local optimum to the best possible compound.

This problem cannot be fully solved by using (V)HTS to find hits from which to begin lead optimization. While (V)HTS searches thousands or millions of starting points, chemical space is so vast, with as many as 1060 molecules, that no compound in a fixed screening library is likely to lie near the global optimum. Moreover, it is all but impossible to predict the quality of the final optimized lead from the starting hit considered by (V)HTS, and only a handful of (V)HTS hits can be subject to lead optimization.

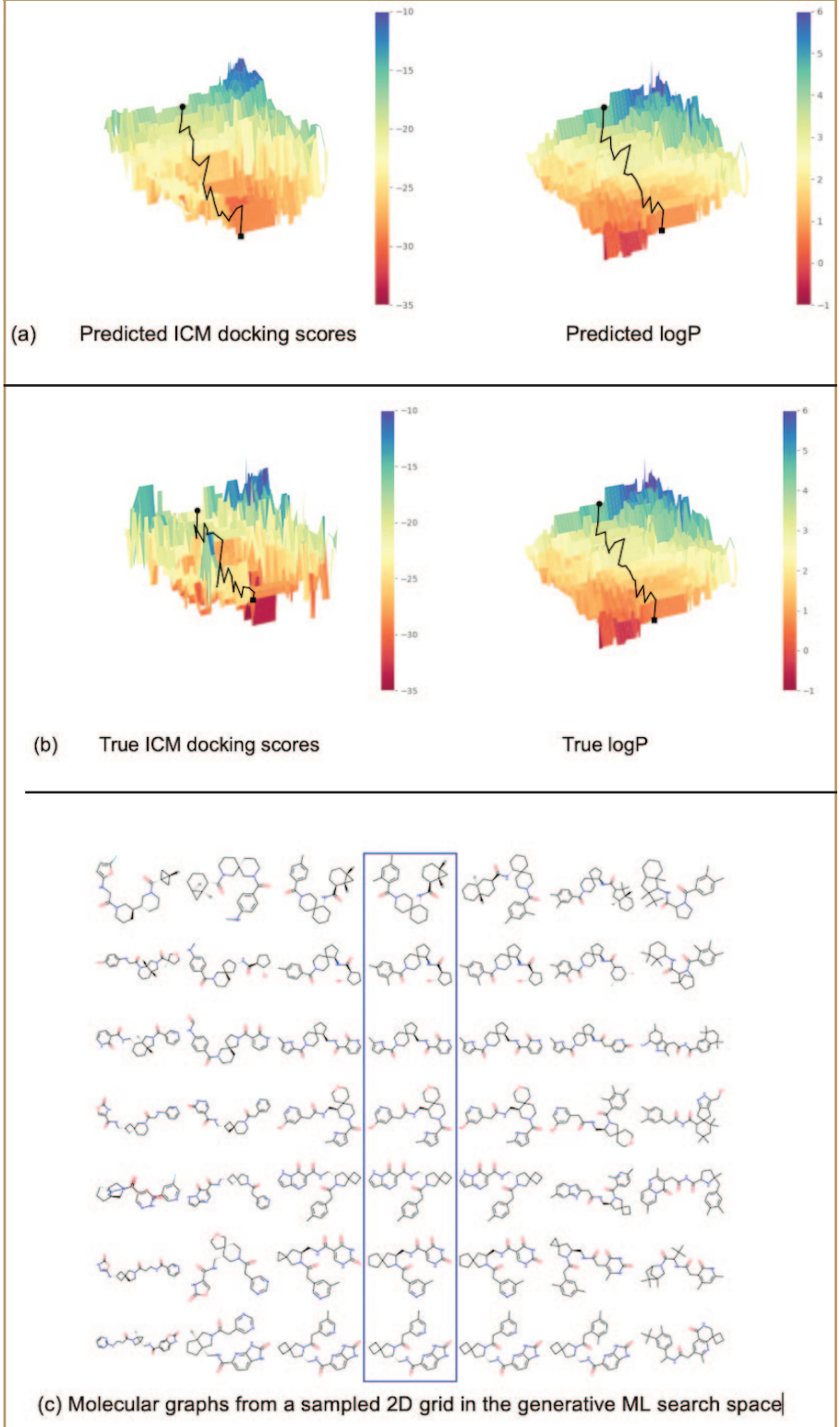
Rather than searching within the native space of molecular structures, generative ML transforms to a learned search space where nearby molecules have similar properties (binding affinity, ADMET, etc), but are less structurally similar, as shown in Figure 2. Conventional drug discovery approaches are like searching for an address in a phone book, where business names are in alphabetical order but geographical location is unordered. Generative ML is like searching for an address on a map, where such spatially-based exploration is intuitive and efficient.

Generative ML constructs this smooth, natural search space by learning a pair of mappings: an encoder from molecules to the search space, and a decoder from the search space back to the space of molecules. The mappings are trained so that molecular properties, such as binding affinity and ADMET, change smoothly with respect to, and can be predicted easily and accurately from, the position in the search space. When properly formulated, with a term encouraging the encoder from molecules to search space to contain no extraneous information, this algorithm is called a variational autoencoder.[12] Deep learning algorithms, such as deep neural networks, are used for the encoder and decoder of such variational autoencoders, to maximize performance.

It is easy to optimize within the search space for many predicted properties jointly, and then map to the associated molecule. Optimization is less likely to become stuck in a local optimum because the search space is much smoother with respect to the properties than the native space of molecular structures. Just as you can find the top of a hill without exhaustively searching its entire surface by repeatedly taking a step in the direction of steepest ascent, optimization within the search space implicitly searches over all molecules that can be represented in the search space. Figure 2 shows such a search space constructed for ICM docking scores of SARS-CoV-2 3CLpro, a computational proxy for binding affinity that can be evaluated exhaustively over a dense grid of molecules.

Other popular generative ML algorithms include generative adversarial networks (GANs).[13] GANs train a decoder mapping from the search space to molecules, so that molecules decoded from random points in the search space cannot be distinguished from real drug-like molecules by another ML algorithm. GANs

FIGURES 2A,2B&2C



Multi-property minimization of ICM docking score and logP in the search space learned by a variational autoencoder. (A) Predicted docking scores and logP, (B) true docking scores and logP, and (C) the corresponding molecular graphs for a 2D slice through the search space. An optimization trajectory through the search space is shown in (A) and (B), and the molecules along the optimization trajectory highlighted with a blue box in (C).

were the first generative ML algorithm to produce high-resolution images, but they suffer from mode collapse: the GAN requires that all generated outputs look realistic, but is satisfied even if only a minuscule fraction of possible realistic outputs are ever generated. Moreover, GANs require severe approximations to accommodate discrete domains like molecular graphs, rather than continuous domains like RGB pixel intensities. While GANs have been very popular for both images and molecules, variational autoencoders offer distinct advantages for drug discovery.

THE IMPACT OF GENERATIVE ML ON LEAD DISCOVERY

Generative ML allows chemical space to be searched more broadly than is possible with conventional techniques. HTS and VHTS are limited to fixed libraries that are small relative to the entirety of chemical space, and are biased toward heavily explored and patented regions. Lead optimization only considers small chemical changes from the hits identified by HTS or VHTS. In contrast, generative ML can search the full extent of make-on-demand libraries with tens of billions of compounds. It can even search over less-explored but still synthesizable regions of chemical space, in which novel chemical matter remains to be discovered, and patents are less dense.

Generative ML can optimize many properties simultaneously within the search space, as shown in Figure 2. Rather than maximizing potency against the primary target alone, as is standard for hit discovery with HTS or VHTS, generative ML can

jointly optimize hits for selectivity, ADMET, and physicochemical properties as well. These critical pharmacological properties are often in conflict; for instance, optimization for potency tends to increase molecule size, lipophilicity, and potency for related off-targets. It is difficult for medicinal chemists to actively balance the effect of a chemical modification against a dozen different criteria; generative ML naturally accounts for these trade-offs.

As a result of this joint optimization, hits identified by generative ML are expected to be more likely to be true, developable hits. Joint optimization for selectivity tends to eliminate assay interfering, reactive, or aggregating compounds because they are unlikely to be selective. Moreover, because jointly optimized hits from generative ML are already designed for selectivity and ADMET from the start, they should be easier, faster, and less expensive to optimize. Altogether, generative ML promises to reduce the cost and increase the speed of drug discovery. ◆

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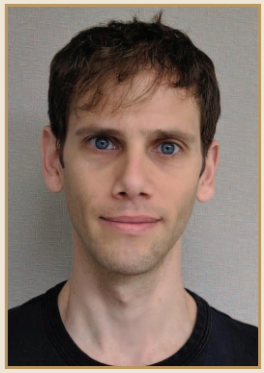
BIOGRAPHIES



Dr. Jason Rolfe is CTO of Variational AI, which uses state-of-the-art machine learning in a data-efficient method to rapidly generate novel and diverse compounds that are optimized for multiple properties to avoid the most common causes of drug attrition and increase the probability of clinical success. Variational AI works with leading biopharmaceutical partners and is developing its own internal pipeline. He earned his BS in Mathematics from the Massachusetts Institute of Technology, his PhD in Computation and Neural Systems from the California Institute of Technology, and spent 2 years as a post-doctoral researcher at New York University studying machine learning under Yann LeCun. He has been conducting research in machine learning for more than 15 years, with a focus on deep learning, generative modeling, and cheminformatics.

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GENE THERAPY

Developing Affordable Point of Care CAR-T Therapies: Expanding Efficacy & Impact

By: Rimas Orentas, PhD, and Boro Dropulić, PhD, MBA

INTRODUCTION

The hypothesis that engineered T cells could recognize and eliminate hematologic malignancies has proven true. The most recent headlines in which two of three chronic lymphocytic leukemia (CLL) patients treated with an anti-CD19 CAR-T cell product remain disease free 10 years after treatment continue to affirm the durable efficacy of CAR-T cell therapy.[1] At the most recent annual meeting of the American Society for Hematology (December 2021), major sessions were devoted to the question as to when CAR-T cell therapy could be moved up to be a second line therapy in adults with B cell leukemia and lymphoma.[2] This would significantly expand the pool of patients eligible for this therapy.

WHAT WE KNOW

A CAR (Chimeric Antigen Receptor) is a cell surface protein expressed on the surface of a cell, introduced by a gene vector. CARs can be expressed on T lymphocytes (T cells), NK (natural killer) cells, and macrophages. T cells exhibit a broad range of activity.

The T cells engineered by means of a gene vector to express a CAR (CAR-T) were initially intended to exert immune effects designed to eliminate cancer cells. However, the field of use has broadened to include the engineering of T-regulatory cells and T cell populations that can remodel tissue. T-regulatory cells can reverse inflammation or auto-immunity in serious human diseases, such as diabetes and rheumatoid arthritis, and also facilitate organ engraftment. Thus, a number of companies focused on CAR-Treg have been founded or acquired CAR-Treg assets, including Sangamo, Sonoma Biotherapeutics, GentiBio, and Abata Therapeutics.

In a remarkable new application, CAR-T cells specific for FAP (fibroblast activation protein, expressed on activated fibroblasts) were shown to reduce cardiac fibrosis in an animal model.[3] This represents a third field of use for CAR engineered T cells, wherein the therapeutic goal is to alter the cellular composition of a targeted tissue.

The primary domain of activity for CAR-T remains hematologic malignancies. All of the currently approved products target either the CD19 protein expressed on leukemia and lymphoma or the BCMA protein, expressed on multiple myeloma. These are: Abecma (idecabtagene vicleucel for multiple myeloma), Breyanzi (lisocabtagene maraleucel, for diffuse large cell B cell lymphopma, DLBCL), Carvykti (ciltacabtagene autoleucel, for multiple myeloma), Kymriah (tisagenlecleucel, DLBCL and pediatric acute lymphocytic leukemia, ALL), and Tecartus (brexucabtagene autoleucel, mantle cell lymphoma)/Yescarta (axicabtagene ciloleucel, DLBCL and follicular lymphoma). The final two listed are essentially the same anti-CD19 CAR-T, but with different applications and slightly different manufacturing, one of which features a T cell enrichment step.

COST OF CARE PROHIBITS WIDE SPREAD USE

One of the major critiques of the currently approved CAR-T cell products is their cost. Drug acquisition costs range from $373,000 to $475,000 and represent the largest component cost of the therapy. A real-world estimate of total costs places the average at $700,000 and can exceed $1 million in some cases (Aislinn Antrim, Pharmacy Times, 2021).

How did we arrive at this astronomical price tag? In past approaches, complex therapeutics in which cells were removed from the body and selected or genetically engineered, the work was carried out in academic medical centers using reagents and de-

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vices that were clinically safe, but not specifically designed as an all-encompassing GMP product. The many different approaches to bone marrow transplantation, implemented at numerous cancer centers, had been the working model for cell and gene therapy to this point. As the process of creating a CAR-T cell generation became more refined and reproducible, pharmaceutical companies stepped in and created a pathway to generate autologous cell-based therapeutic products.

While a boost to the field with regard to interest from investors, there are drawbacks. By adopting a large-scale central manufacturing model, new innovations are potentially stifled, as corporations have to recover the extraordinary costs devoted to creating what is essentially a first-generation product. Moreover, these first-generation products are not as efficient or effective as the T cells bearing the CAR are over-activated and differentiated, leading to decreased efficacy in the body.

FINDING A BETTER WAY

The following presents three pillars by which efficacy and impact can be increased, and by which costs can be significantly lowered, leading to greater availability of CAR-T products for all those who would benefit. The first is using a place-of-care method for CAR-T production, the second is the advent of extremely short CAR-T generation protocols, and the third, while still on the horizon, has the ability to upend the entire field. Generation of CAR-T by direct injection of gene vector particles into the body, allowing for transduction, activation, and expansion CAR-T, would entirely alter how we approach cell and gene therapy.

PLACE-OF-CARE MANUFACTURING FOR CAR-T

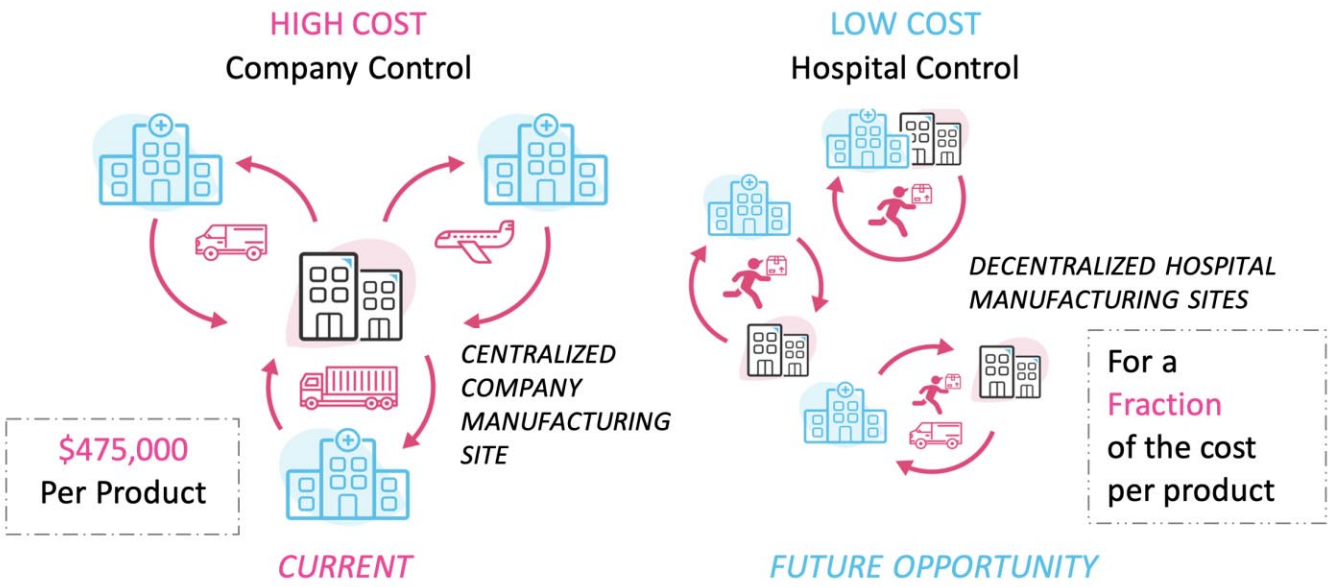
The current approved therapies for CAR T cell production require extensive logistical and regulatory support. When patients are approved to receive CAR-T cell therapy, they first undergo apheresis (leukocytapheresis/leukopheresis), a procedure whereby a patient is connected to a medical device that receives whole blood from a vein, the white cell fraction of the blood (leukocytes) is harvested by means of differential centrifugation, and the red cell fraction returned to the patient. Apheresis is a costly step requiring dedicated personnel and devices. The advantage is that far more white blood cells (lymphocytes) can be collected than from a normal blood draw. Once collected, the leukocytes are processed, frozen, and then shipped to a central manufacturing facility. There, the cells are thawed, processed, and transduced with a retroviral or lentiviral gene vector. Once transduction has taken place, and the engineered cells pass release criteria (such as sterility and evidence of CAR expression), they are repackaged and shipped to the clinical site for infusion into the patient.

Caring Cross proposes that the economics of place-of-care manufacturing will continue to grow in importance, both in the current US market, and across the world. The argument or challenge against place-of-care manufacturing usually centers on reproducibility. In order to demonstrate that place-of-care manufacturing can be robust and reproducible, we tested CAR-T production in two geographically disparate sites using identical manufacturing platforms, reagents, and lentiviral vector (LV).

Very similar CAR-T were manufactured and used to treat patients at both Case Western Reserve/University Hospitals Medical Centers in Cleveland, OH, and the Dimitry Rogachev Pediatric Cancer Hospital in Moscow, Russia. These place-of care products were generated in a much shorter time than commercial products and were used to treat patients who had more severe disease (and could not wait the weeks required for central manufacturing of CAR-T).[4] Our experience with other sites employing place-of-care manufacturing show similar high-quality products being produced with exceptional outcomes.[5] Using a closed system, the cell manufacturing steps in these trials were carried out in the bone marrow transplant laboratories, and thus in a controlled environment, but outside of a traditional clean room. This has great implication for cost savings. Using the closed manufacturing devices, currently available on the market, allows a center to operate with minimal reliance on a clean room suite, Figure 1.

The use of place-of-care manufacturing has been essential in the manufacturing of CAR-T cell products outside the US. Not waiting for costs to drop on their own, Spanish investigators formed a national network, generated their own LV, and a employed a commercial cell production platform (CliniMCAS Prodigy, Miltenyi Biotec). Hospitals were able to produce CAR-T products for B cell malignancies at a greatly reduced cost that had similar clinical benefit as current commercial products.[6] National healthcare systems across the globe are taking note of this approach, and it will surely expand. The UK government has collected comments and will soon issue guidance for place-of-care manufacturing.[7] This will establish the needed regulatory framework and poten-

FIGURE 1



Combining technology, distributive manufacturing, and place-of-care production significantly reduces cost of cell therapy products. On the left side, the current high-cost process with central manufacturing is illustrated. On the right side, a distributed model with local production that does not require the complex custody, regulatory, and shipping logisitics required for a centrally manufactured product. Manufacturing could occur at a regional center serving a number of local institutions or be housed directly in the hospital.

tially place the UK in the lead for both CAR-T production and innovation.

SHORT CAR-T GENERATION PROTOCOLS

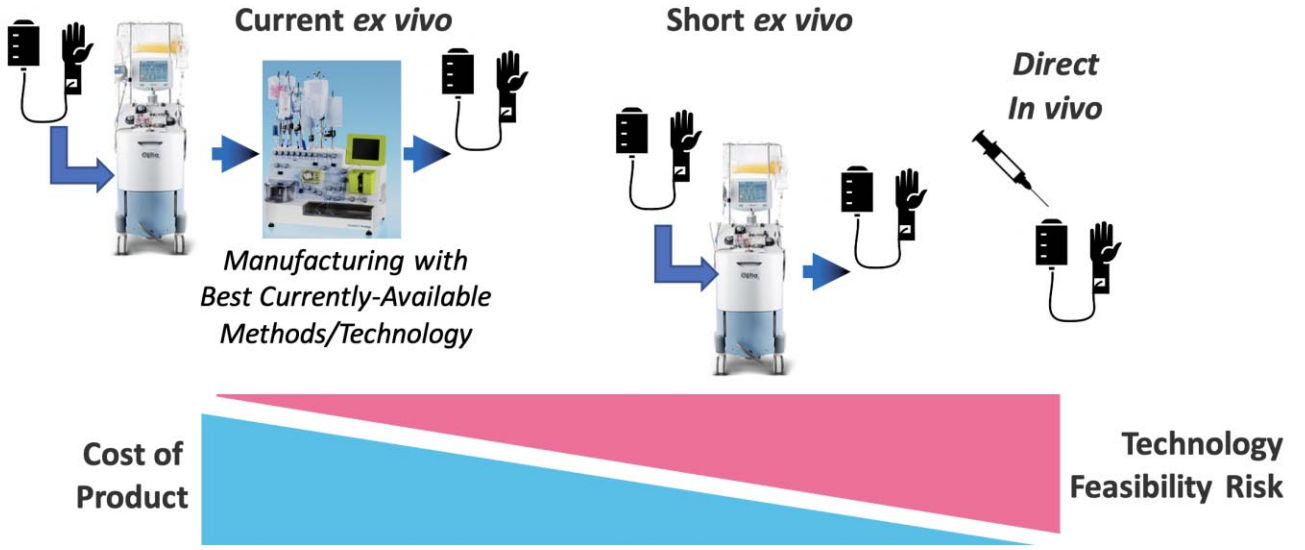
The creation of CAR-T cell products outside the body is a complex and lengthy process. Putting the logistics of where the CAR-T cells are produced aside, the manufacturing process can be 8 days or longer. At the production facility, the CAR-T cell production process starts with the isolation of either total leukocytes (PBMC) or selection for CD4 and CD8 T cells by immunomagnetic bead selection. Isolated T cells are then activated with reagents designed to cause cell activation and expansion (ie, Dynabeads CD3/CD28 CTS™, Invitrogen; T Cell TransACT™, Miltenyi Biotec; GMP Cloudz T Cell Activation Kit, R&D Systems). This set-up process usually takes a single day, followed by transduction with a lentiviral or retroviral gene vector that encodes the CAR. This adds another 2-3 days. The subsequent 5-9 days of culture allows for CAR-T to expand to sufficient numbers for formulation for either infusion or cryopreservation. The media and supplements (including cytokines like IL-2, IL-7, IL-15, or IL-21) must also be clinical grade and add to the costs.

Regulatory agencies require some evidence that the T cells treated with a gene vector do not carry along with them sufficient amounts of plasmid used during production of the gene vector (usually a PCR-based test) to be expressed in the host. Also the product is tested for the absence of replication-competent virions (termed RCL, replication competent lentivirus) arising from recombination of genetic elements. While RCL has never been observed in a clinical process, samples must at least be retained in order to allow for subsequent testing.

Investigators have been working to decrease the culture time following transduction with LV. The barriers have been both regulatory and methodological. The regulatory hurdle seeks to quantify the amount of residual elements used during CAR-T manufacture that are carried forward into the infusion product. The methodological challenge is to prove that the CAR is indeed now being expressed by the transduced T cell population. In addition to these concerns, it is well recognized the longer T cells are cultured the more "differentiated" they become. A differentiated T cell has decreased ability to expand and exert activity against diseased tissue.

A recent publication from Dr. Milone's lab at the University of Pennsylvania took all of these challenges straight on and created a single-day CAR-T generation process that is not dependent on the addition of a T cell stimulation reagent.[8] Although, a regulatory path forward has yet to be determined, the methodological barriers to ultra-rapid CAR-T production are

FIGURE 2



Moving to a low-cost cure platform with the advancement of new improved technologies. Illustrated is the increasing risk (left to right) as we move from the current known ex vivo process, and toward a direct injectable, that has yet to be accomplished but is the current focus of intense research and development activity. The advent of a directly injectable vector would entirely upend the current processes that are highly dependent of cell manipulation *ex vivo*.

falling rapidly. The ability to create a CAR-T product in a single day renders the complexities of a central manufacturing approach essentially a moot question. It is no longer worth the trouble.

DIRECT *IN VIVO* APPLICATION OF GENE VECTORS TO PRODUCE CAR-T

Given the onset of ultra-rapid generation of CAR-T outside the body, the next logical step is to do away with cell processing outside the body entirely, and to directly inject gene vectors (Figure 2). For such a vector to be successful, it would need to have both selective targeting/transduction of the intended T cell population, as well as some mechanism to expand or select for transduced cells once the gene vector has been administered.

A recent entrant to the field, Umoja Biopharma, is proposing to generate CAR-T with a vector particle that can be directly injected to the body, and which binds to target T cells by virtue of a specific receptor in the particle outer membrane. In addition to a CAR, the payload within the gene vector includes a rapamycin-activated signaling protein that initiates IL-2 like signaling in the transduced T cells. Rather than encoding a "driver" like signaling protein, companies like Enochian BioSciences endow their gene vector with a drug-resistance gene, in this case to the drug cyclophosphamide. Cyclophosphamide is used in CAR-T therapy to reduce endogenous immune cells and allow for CAR-T expansion. Enochian will take advantage of this process by using the drug for in vivo selection of transduced cells.

While targeting the LV to the right T cells and providing for a method of selection or expansion is essential, one more barrier may yet remain. It appears the most common envelope protein (the protein on the lentiviral vector surface that allow for entry into the targeted cell) VSV-G, can be inactivated by serum complement. Fortunately, researchers at the Fred Hutchinson Cancer Research Center have developed a new envelope protein that can be used instead of VSV-G, derived from the Cocal virus.[9] Thus, use of Cocal envelope protein in lentiviral vector production, combined with preferential targeting and selection, will soon bring the era of direct LV transduction in the body to pass.

Given the rapid development of the field, other instantaneous methods of gene transduction, such as electroporation with Crispr-based gene modification, will also play a role but will likely remain a process carried out on cells outside the body.

SUMMARY

The commercialization of CAR-T manufacturing was a watershed moment in cell and gene therapy. What was once a process limited to highly skilled and re-

source-rich academic medical cells was now made available to any medical center with cell therapy experience, essential a center THAT has a track history in bone marrow transplantation. However, the high price for central manufacture of CAR-T has important limitations to its long-term use. The high price for CAR-T products makes them unavailable in low- and middle-income countries, and for individuals with inadequate healthcare coverage in high-income countries.

This represents a serious justice issue. These therapies were developed using many public resources (such as NIH-funded comprehensive cancer centers, and IP developed in public institutions). If the benefit of these therapies are available only for the economically elite, public trust in medical science will be undermined. In addition, while the learning required to create a commercial product featuring genetically engineered cells was impressive, the costs to setting up these systems creates a competitive landscape against new innovative technologies that could drive down cost. And finally, the technology and the regulatory framework required to safely oversee the development of CAR-T therapy continues to evolve.

The future belongs to those who will be able to innovate rapidly, maintain regulatory confidence, and drive down costs in order to make CAR-T cell and other engineered cell therapies available to all who would benefit. ◆

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BIOGRAPHIES

Dr. Rimas Orentas is the Co-founder and Scientific Director of Caring Cross. He earned his PhD from The Johns Hopkins University School of Medicine. After 12 years in academia, he worked for 5 years at the Pediatric Oncology Branch of the NCI, and for a total of 5 years at Lentigen Corporation, where he served as Scientific Director. He currently is an investigator at the Ben Towne Center for Childhood Cancer Research, Seattle Children's Research Institute, Director for Scientific Integration at CureWorks, and Professor of Pediatrics and Laboratory Medicine and Pathology at the University of Washington School of Medicine.

Dr. Boro Dropulić is the Co-founder and Executive Director of Caring Cross, an organization focused on improving business models to support the affordability and accessibility of gene therapy products. Dr. Dropulić earned his PhD from the University of Western Australia and his MBA from the Johns Hopkins University (JHU). He has been in the gene therapy field since the late 1980s.

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Bill Hartzel

Senior VP & Head of CDMO Business

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Drawing on this fundamental experience, its contract development and manufacturing organization (CDMO) business has supported the development and manufacturing of over 40 commercial and more than 100 clinical biologic programs for their biopharma partners.

Drug Development & Delivery recently interviewed Bill Hartzel, who joined the company in March 2022 as Senior Vice President and Head of CDMO Business, to discuss the company's plans for current and future CDMO operations and client partnership opportunities.

Q: What is biopharma looking for in a CDMO, and how does Emergent CDMO play a role?

A: Biopharma's product pipelines for novel and next-generation biologics-based therapeutics and vaccines are continuing to grow as we see more drugs being developed for rare and orphan indications. Many of these new molecules are coming from smaller, "virtual" organizations, and as a result, biopharma companies continue to seek new opportunities to leverage the industry's expertise, engaging outsourcing partners to support their process and formulation development activities to enhance and accelerate their drug substance and drug product manufacturing.

To meet the development and manufacturing needs for these novel biologic platforms, biopharma innovators are looking for the right fit for their products – the relevant expertise, integrated capabilities, and flexible capacity in place to support

the development, technology transfer, scale up, and manufacturing of these novel molecules. This is where Emergent CDMO stands out as a strategic partner for the development and manufacturing of complex biologics. Emergent CDMO provides valuable insight and perspective, based on our proven expertise from developing and commercializing our own novel products.

Foundationally, the CDMO and biopharma partnership is based on trust, communication, and delivery. These are three intertwined pillars at the heart of a strong CDMO partnership and what biopharma customers are seeking. With any development or manufacturing program, challenges can arise, and unexpected outcomes may occur. And while these events may not be ideal for either party, a true partnership is forged by overcoming these hurdles together. High levels of transparency and communication not only help build a strong understanding of the specific program needs, but also help overcome any obstacles that may occur during development and manufacturing.

Strong collaborations are constructed through transparent communication, program expectation alignment, and importantly, consistent delivery on programs' expectations. Partnering with an experienced CDMO that understands the challenges and demands of bringing a product to market, as well as having deep technical and regulatory expertise with a range of technologies, processes, and products can offer advantageous guidance and solutions to accelerate the therapy to the market.

As a dedicated and supportive CDMO partner, clients can leverage Emergent CDMO's flexible capacity, integrated solutions, and experience to support the clinical and commercial successes of their molecules.

Q: What trends are you seeing in the industry?

A: What we are seeing, and what I'm excited about, are the changes in efficiency and productivity during development and manufacturing operations. The growth of novel therapeutics and vaccines are driving technological advancements and flexibility in bioprocessing, such as productivity enhancements through automation, isolator technologies, and the continued adoption of single-use systems.

In addition to bioprocessing enhancements, we are also seeing new drug formulations to improve therapeutic efficiency and drug delivery, such as lipid nanoparticles (LNPs), which are requiring advanced expertise and solutions for the development, formulation, and manufacturing of these complex molecules.

In fact, to address these novel therapeutic manufacturing needs, we proactively invested over $150 million in capability expansions across multiple sites to provide additional drug product manufacturing automation and capacity. We have also invested in automated capabilities for biologics development. These investments have allowed us to meet the changing needs of our clients and provide much needed capacity for current and future market demands.

Q: Can you provide some additional detail on the recent expansions and investments?

A: These investments are in our core areas of the CDMO business. In development services, we have added several new high-throughput instruments affording robust development and optimization for drug substance and drug product process development and scale-up. A strong focus for us has been on maximizing automated systems for bioreactor optimization, as well as resin and membrane screening, which can accelerate the overall development timeline for our clients. Our investments in pilot- scale lyophilizers, nanoparticle formulation, and process development equipment have allowed us to meet the growing industry-wide demand for lyophilized and nanoparticle products, such as LNP formulations for mRNA products.

On the drug product side, we have significantly enhanced our aseptic fill/finish capacity and capabilities. Our three new isolator-based, flexible fill lines provide enhanced sterility assurance with minimal operator interventions and ready-to-use (RTU) pre-sterilized vials and syringes or an integrated vial washer and dryer. The lines have distinct capabilities: the FlexPro 50 line features an integrated, auto loading/unloading lyophilizer, the Integra line provides biosafety level 2 (BSL 2) containment for viral products, and the VanRx line houses a fully contained, robotic system to support the production of small-batch size next-generation therapies. In addition to these fill lines, we have added two automated visual inspection systems, a semi-automated visual inspection line, as well as a high-speed fully automated packaging line that includes labeling, cartoning, and serialization.

In drug substance, we continue to enhance our facilities and processes by leveraging single-use bioreactors (SUBs) and technologies during both process development and cGMP manufacturing activities, allowing for simplified scale-up and tech transfer while adding flexibility to meet our clients' needs as they evolve from development to commercialization.

Q: What makes Emergent CDMO different from other CDMOs?

A: Emergent CDMO is unique in this space given we are an integrated CDMO that's built on Emergent's existing foundation of development, manufacturing, and regulatory excellence. Being an integrated CDMO, we know what we need in a manufacturing network, how to build expertise and capabilities, and subsequently offer that to the market. Our experienced teams have the knowledge to help anticipate what's coming next, proactively communicate, and adapt to any changing needs. In addition, we have the experience needed to provide process and infrastructure insights that can help avert unnecessary and costly delays. This distinctly positions us to be able to focus directly on our clients and their successes.

Our CDMO business leverages the talent, capabilities, and expertise from across the organization to support the development and manufacturing needs of our biopharma clients' complex biologics. In addition to a tremendous team of manufacturing science and technology experts, our quality, regulatory, and compliance professionals have the experience required to support our customers though the hurdles of development, scale-up, and change management of the manufacturing process of their clinical and commercial programs.

Another unique position is Emergent's history and long-standing business in delivering protections against public health threats. This experience is particularly beneficial for biopharma clients whose products are supported by governments and NGOs to meet a critical medical need or address public health threats. And with a growing demand for drugs that focus on public health threats and the recognized need for pandemic preparedness, having that background in working with governments throughout the world is not a typical proficiency found at a traditional CDMO and is an area we can provide valuable expertise.

The unique expertise, knowledge, and systems designed to handle the rigorous requirements of working with different governments and other agencies coupled with our technical knowledge in working with complex biologic molecules allow us an opportunity to provide integrated offerings and tailored approaches for a variety of viral and non-viral products to support our clients' diverse needs. We understand first-hand what it takes to bring a drug from development through to commercialization, and there's no substitute for that experience.

Q: How is Emergent CDMO positioning itself as a strategic partner?

A: As we move past the urgent pandemic response required for COVID-19 vaccines and therapeutic production, we are able to take a step back and evaluate how we can become an even stronger strategic CDMO partner for our current and future biopharma clients. This includes monitoring the market trends and changes in the regulatory landscape and evaluating our internal capabilities and processes to support the growing needs in the market.

In this new era, we will continue to leverage our proven expertise in viral and non-viral platforms to focus on simplifying the supply chain for our partners and streamlining the integration of our end-to-end CDMO solutions for molecule-to-market biologics. Our end goal as a strategic CDMO partner is to accelerate our biopharma clients' complex molecules to market through our demonstrated expertise and integrated capabilities: from process development to commercial production.

To enhance these capabilities, we will be focusing on harmonizing our processes and systems across our CDMO manufacturing network, allowing us to provide consistent quality processes and business operations to our clients. This approach, with integration across drug substance and drug product, serves to benefit our clients as their product moves through the molecule-to-market pathway: from development services to drug substance to drug product manufacturing.

Our ultimate goal as a CDMO partner is to provide trusted, quality-focused operations that seamlessly deliver on the aligned expectations, allowing our clients to fully focus on the patients they serve. Thus, fulfilling both companies' missions: to bring life-saving, life-extending therapies to patients around the world.◆

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- Clinical to Commercial
- Deep Cold Storage
- Digital Health
- Human Factors
- Manufacturing
- New Technologies
- On-Body Delivery Systems
- Regulatory Affairs and Standards
- Sustainability of Devices

Don't miss the return of the largest global conference on drug delivery devices to an in-person format to take advantage of networking opportunities and the chance to connect with numerous vendors and suppliers in the Exhibit Hall!

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POLYVINYL ALCOHOL, UNSPECIFIED **(Tablet/Capsule coat)**	11.72 mg
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TALC **(Tablet/Capsule coat)**	4.33 mg
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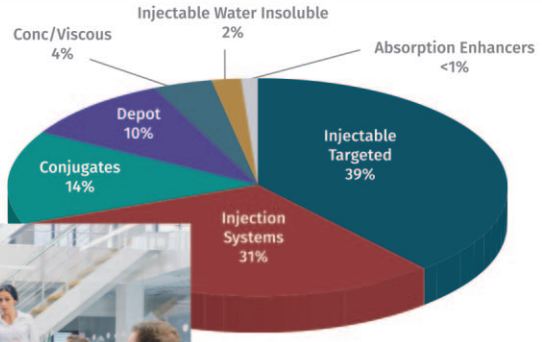
TITANIUM DIOXIDE **(Tablet/Capsule coat)**	7 mg
FD&C RED NO. 40 **(Tablet/Capsule coat)**	
FD&C BLUE NO. 2 **(Tablet/Capsule coat)**	

Evaluate New and Promising Technologies



Injectable Drug Delivery Technologies

Screen Potential Partnering and Investment Opportunities

Select Companies

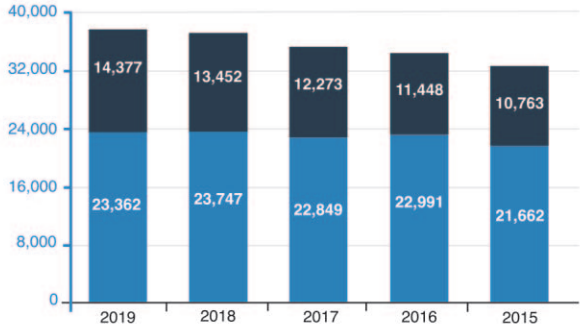
Amgen Inc. x

Biogen, Inc. x +

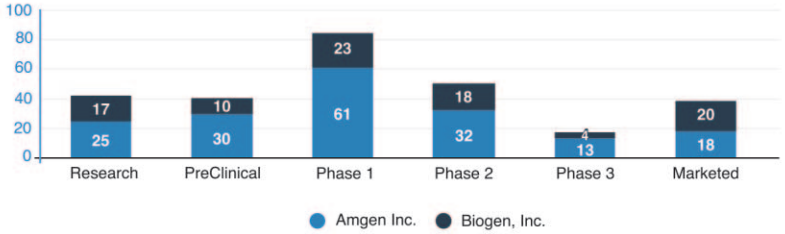
Attribute Type

- Gross Profit
- Net Income
- Number of Employees
- Operating Income
- Research and Development Expenses
- Sales, General and Admin. Expenses
- Total Assets
- Total Current Assets
- Total Current Liabilities
- Total Equity
- Total Liabilities
- Total Revenue

Annual Data



Product & Pipeline Count



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Special Feature

Injection Devices: Three Trends Influencing Development & Delivery

By: Cindy H. Dubin, Contributor

The global injectable drug delivery market reached $15.13 billion in 2021 and is projected to reach $83.38 billion in 2030.[1] Industry experts point to three key reasons why the sector is poised for such phenomenal growth. First, is the increase in self-treatment stemming from the pandemic as people chose to avoid hospital settings. "The rise in self-administration means that patients require devices that are simple and intuitive to use while fitting into their daily lifestyle," says Michael Earl, Director, Pharmaceutical Services, Owen Mumford Ltd.

Linked to self-treatment is the second trend impacting delivery device development: digitization. The addition of connectivity provides patients with prompts, injection guidance, and dose confirmation as well as allows healthcare practitioners both access to this data and the ability to monitor and intervene as required to help improve medication compliance.

While connected electronic devices do have benefits, they also pose the challenges of appropriate disposal after use, claim industry gurus. Thus, there is an increased focus on sustainability and environmental stewardship – the third factor influencing the market. This has led to the need for devices with improved sustainability credentials, which can be demonstrated by life cycle analysis, as well as an increased focus on reusable devices as opposed to disposable alternatives.

This annual *Drug Development & Delivery* exclusive report showcases how various device manufacturers are addressing these trends in their injection designs.

Catalent Biologics offers automated assembly of autoinjectors, safety devices, and accessorized prefilled syringes for both clinical and commercial supply, all fully integrated with drug product manufacturing.

Artcraft Health: Ensuring Certainty of Use

The development of combination medicines, biologics, and biosimilar compounds is on the rise. The successful use of these novel and life-saving drugs has become increasingly dependent on innovative and cost-effective delivery methods, such as autoinjectors, on-body injectors, and other devices that support patients' functional and lifestyle needs.

However, along with these new developments and innovations comes the need for appropriate educational support for both healthcare providers and patients to ensure these new drugs and delivery methods are adopted, accepted, and used properly.

"We believe that tailor-made educational programs and demonstration devices are critical for long-term success," says Marty Mason, Senior Director of Demonstration and Training Devices at Artcraft Health. "Our primary goal is to elevate and support the entire patient experience through educational onboarding initiatives involving both clinicians and patients. These factors are critical to the launch of a new or alternate delivery method."

Artcraft Health applies educational design, adult learning principles, and a proprietary approach to health literacy during the process. "Being a leading health education and engagement agency, the company is dedicated to ensuring a therapy's certainty of use," says Mr. Mason. The focus, he says, is to help patients, caregivers, clinicians, and healthcare providers – who are either counseling patients or adopting new therapies and drug delivery methods – to build the skills, knowledge, and motivation they need for a successful outcome.

Artcraft Health simplifies complex delivery methods and packages them into easy-to-understand educational materials and guides patients to comply with dosing and administration. "Our holistic approach to demonstration device development and training not only provides the highest quality device but also aids in the launch strategy for commercial teams," he says.

Services include developing demonstration devices such as prefilled syringes, autoinjectors, and on-body injectors, as well as training kits, onboarding initiatives, and educational materials across all media. Artcraft Health also provides the documentation that supports these devices, such as instructions for use, quick reference guides, packaging, cold chain logistic packaging, and training infusion kits. Current clients include AbbVie, Alexion/AZ, Amgen, Fresenius-Kabi, Merck, and Takeda.

Catalent Biologics: Design With the End User In Mind

There is increasing interest in customized designs capable of delivering a wider variety of medications, as well as more user-friendly, off-the-shelf options, says Shanna Stevens, Senior Manager, Manufacturing Technology Packaging, Catalent Biologics.

"Customization is key for patients that need a targeted approach to their treatment, and this applies to the design of features useful to both the caregiver and patient, combined with the core capabilities of the device, to optimize delivery of the injectable formulation," she says. "This allows patients with limited dexterity to self-administer treatments as well as those who require the safe delivery of larger dose volumes."

Designing an injector device with the end user in mind starts by knowing who will administer the drug and what the medication is treating. "If a medication is treating a person with dexterity issues, then the design must be easy to open and use, while still maintaining sterility and security

through features such as tamper evidence," says Ms. Stevens. "Additionally, some treatments require delivery of large volumes or fills that have a high viscosity, both of which can take longer to dispense. This must be considered when choosing the design and make-up of the drug delivery system."

Congruence Medical Solutions: Innovative Devices to Solve Compelling Problems

New scientific and market "frontiers" drive changes in drug delivery, and ophthalmology is an example where frontiers are creating compelling drug delivery problems. The ophthalmic injectable pipeline has grown and diversified recently, with more target diseases (e.g., Diabetic Macular Edema, Geographic Atrophy), more potential delivery routes (e.g., subretinal, suprachoroidal), and more varied dosing frequencies. New delivery needs have therefore arisen, such as microliter dose accuracy, minimizing leachable silicone, and viscous formulations. Simultaneously, retinal surgeons want to increase patient throughput, while maintaining sterility and manual injection control.

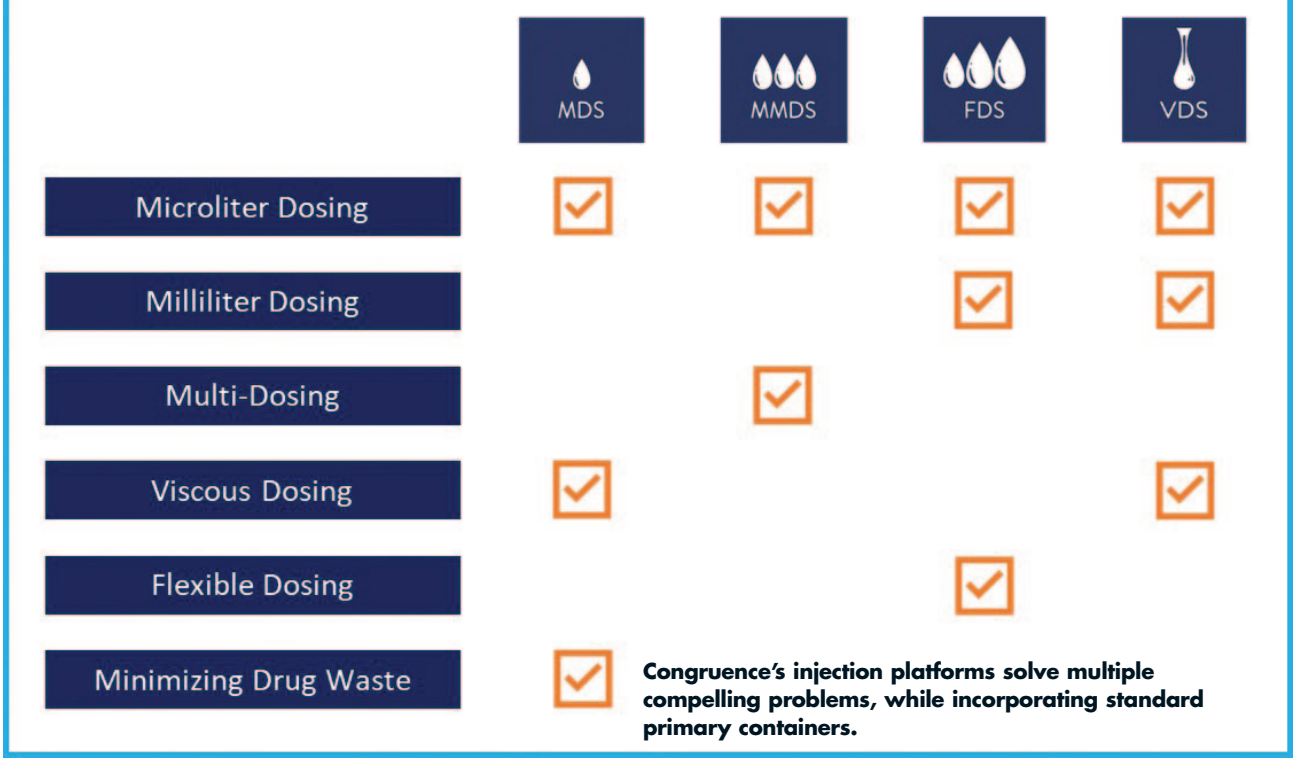
Congruence has partnered with multiple pharma companies to address these changing ophthalmic injection needs. The result is Congruence's Microliter Dosing Syringe (MDS) module, which attaches to any standard prefillable syringes. It improves safety, ease of use, and efficiency by enabling simple dose setting and priming, accurate microliter dosing, reduced injection force, and reduced drug waste, says Richard Whelton, Head of Marketing and Business Strategy at Congruence.

There are multiple other areas outside ophthalmology where market and scientific frontiers are creating compelling needs:

Viscous Drugs – Increasing viscosity of pharmaceutical formulations is a well-known trend, and conventional devices struggle to inject these drugs. Even non-viscous drugs may encounter similar injection issues if the drug is injected too soon after refrigeration removal or a fine injection needle is required.

"Pharmaceutical companies often increase dose volume to counter formulation viscosity, which leads to less patient-friendly delivery solutions such as multiple injections or expensive wearable injectors," says Mr. Whelton. "This may reduce patient compliance."

Congruence's Viscous Dosing technology addresses this issue by enabling highly viscous drugs (up to 3000cP) to be injected in a single dose. This technology has been incorporated into a manual syringe dosing



Congruence's injection platforms solve multiple compelling problems, while incorporating standard primary containers.

module, and a newly developed autoinjector with integrated safety and ease-of-use features for home use.

Flexible Dosing Volume – More focus is being placed on varying injectable drug dose volumes easily and accurately. Examples are potent immunotherapeutic agents that require weight-based dosing for safety and efficacy, and dose ranging studies during clinical trials. Variable dosing can also expand access, such as to pediatrics that require non-standard dose volumes. Congruence's Flexible Dosing Syringe module delivers variable volumes over a range (50µL-2.2mL), beyond what is possible with pens, says Mr. Whelton.

Microliter Dosing – An increasing number of therapies require small dose administration, such as with targeted delivery and cell and gene therapies. "Standard syringes cannot deliver at the required accuracy, so a device such as Congruence's MDS module is preferable," he says. Furthermore, some small dose drugs, such as intra-tumoral and dermatology drugs, require delivery of multiple doses to the same patient. Congruence's Microliter Multi-Dosing Syringe (MMDS) module can deliver each separate dose accurately with a simple one-step push for convenience and safety.

Credence MedSystems, Inc.: Enabling Precise Injections of Viscous Fluids

Credence has been responding to very clear trends in the novel drug delivery market for ocular and medical aesthetics applications. A shared characteristic in these markets is the use of very fine needles for injection into sensitive areas. Additionally, there is a trend towards more viscous injectables, both into the eye as well as into the face. At times, a single injection is required, while at other times multiple injections from the same syringe are warranted. Finally, certain applications require extremely low-volume injections and have the requirement for high accuracy and precision.

These competing requirements present significant challenges (and significant opportunities) for the device to enable a user-friendly experience that allows safe dosing. For example, the higher forces associated with injecting viscous liquids are exacerbated significantly by the requirement for fine needles. Similarly, achieving highly accurate and precise injections is more challenging with very low micro-volume doses. "Credence's platform of Metered Dosing solutions aims to address these challenges, and in some cases, to enable the delivery of a drug that would otherwise not have been able to be successfully administered," says John A. Merhige, Chief Commercial Officer, Credence MedSystems, Inc.

Credence's Micro-Dose™ Injection System delivers a single injection in the micro-liter range. Applications for this can be found in the anti-vegf and gene therapy space. The Multi-Site™ Injection System allows multiple injections of a pre-determined dose, for use in toxin, filler, and dental applications. Force-Assist™ can be applied to either technology in order to reduce the force required to administer the injection to a fraction of what would otherwise be required. Mr. Merhige says: "This opens up opportunities for users to comfortably inject viscous fluids through small needles when previously the force required would have been preventative."

He concludes: "Credence is ad-

Credence's Micro-Dose and Multi-Site injection systems enable precise dosing of single or multiple injections of very low volumes.

vancing these product lines and additionally has been working with multiple pharmaceutical customers to combine various elements of these technologies into a solution that addresses the requirements of unique and novel applications."

DALI Medical: Usability Elicits Safer Operation

Today, drug delivery solutions need to be patient-centric. Increasingly, new drugs are being developed for subcutaneous self-injection by patients and family caregivers. In response, new drug delivery devices are being designed for easy usability, high user safety, and patient comfort. To ensure patients' and caregivers' needs are optimally addressed, it is vital to seek their input during device development.

"Device design should include all inputs evolving out of human factors and usability studies analyses," says Ziv Cahani, VP Business Development and Marketing, DALI Medical. "And testing should be conducted with varied user groups to ensure that all needs are considered and implemented to mitigate the risks."

Beyond the paramount need for patient and user safety, injectable drug delivery devices are increasingly incorporating features that improve the patient experience. For example, devices are being designed with features that mitigate needle phobia and real and/or perceived pain. Additionally, digital devices provide push notifications to keep patients engaged. "By closely considering and analyzing human factors' input, it is possible to design better drug delivery devices, i.e. devices that improve compliance," says Mr. Cahani.

DALI Medical offers a range of advanced injectable drug delivery devices for clinical trials and commercial drugs administered by healthcare professionals and self-injected by patients and caregivers. DALI's devices enhance safety, ease-of-use, reducing pain and perceived pain, and mitigating needle phobia, he says. DALI injection devices can be used for virtually any therapeutic area that could be treated by subcutaneous and/or intramuscular injections.

DALI device features and functionality address different aspects of the user experience that are vital to compliance, Mr. Cahani adds. "Our devices are safety-engineered to protect users and patients and provide high usability. Enabling self-injection can have a major effect on compliance as it is more convenient for patients. Supporting this, we offer devices with automatic needle insertion that facilitates self-injection and hidden needle capabilities that minimize patient anxiety." Additionally, DALI offers devices that issue and/or display reminders and alerts that help keep patients engaged and make it easier for patients to keep up with the treatment regimen.

A customized version of DALI Medical's SAN-Light passive safety needle enables the self-injection of a new, super-high-viscosity drug, while enabling a high level of safety and minimizing needle phobia anxiety. DALI customized its SAN-Light safety needle to meet viscosity challenges, regulatory requirements, and user preferences.

DALI's customized SAN®Light safety needle offers an easy-to-use injection device for high viscosity injectable drugs.

Eitan Medical's Sorrel™ wearable drug delivery platform reduces the number of user steps, which minimizes the risk of error.

Eitan Medical: Smart, Connected Device Meets Industry Trends

'Smart' injection devices that allow for a more sophisticated administration experience are in demand following the development and introduction of novel injectable medications to market. Such devices need to meet specific requirements related to device performance, allowing for larger injection volumes and higher viscosities of biological drugs. In addition, devices supporting the shift from hospital to home are required as well, so drug delivery devices should be designed to meet usability aspects of the self-administration and home-care market.

Eitan Medical provides safe, intuitive, and flexible infusion and drug delivery solutions designed to address these trends. The devices aim to improve patient and clinician quality of life across the continuum of care, including in hospital, ambulatory, and home care environments, says Mindy Katz, Vice-President, Marketing and Alliance Management at Eitan Medical.

"All of Eitan Medical's products are software-controlled, connected, electro-mechanical devices, intended to support the evolving drug delivery market," she says.

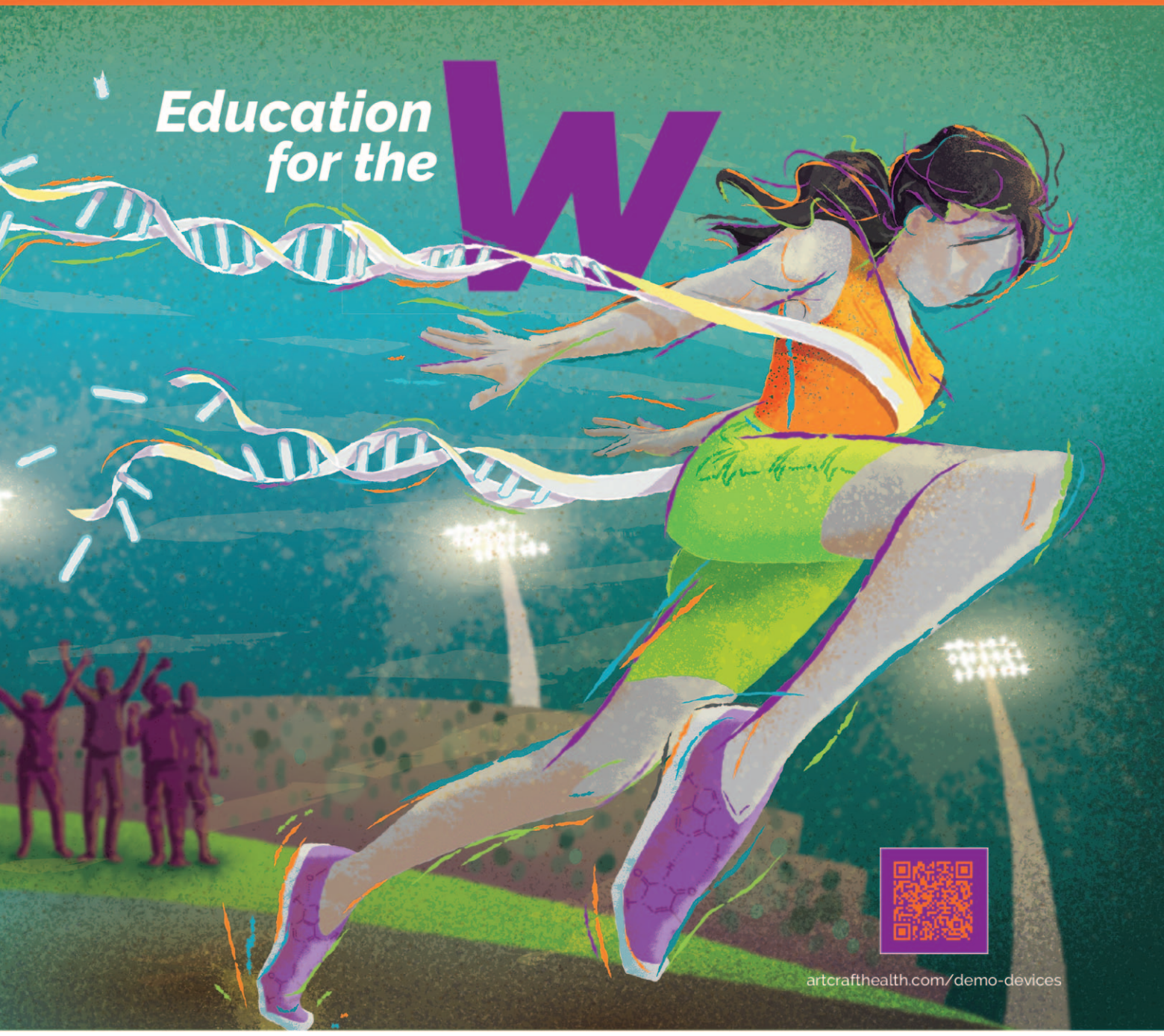
From the patient perspective, a key aspect to ensuring treatment compliance is overcoming usability challenges related to the drug delivery device. For Eitan Medical's Sorrel™ wearable drug delivery platform, this includes reducing the number of use steps, which minimizes the risk of user error. One example of a technical feature that does just that is the internal ultraviolet LED chamber that allows for disinfection at point of care, removing the need to swab a vial or cartridge prior to drawing liquid from it. Moreover, Eitan Medical has added smart sensor technology, coupled with integrated algorithms to ensure that treatments are being delivered safely to patients in home environments. The technology provides an indication to the patient on the status of the treatment, automatically tracking a variety of technical parameters throughout the self-administration process.

In addition to designing devices that are easy for patients to use, Eitan Medical assists its pharmaceutical partners in bringing novel medications to clinical use and market sooner. Ms. Katz says: "By having the Sorrel platform conform to a variety of primary containers, pharmaceutical manufacturers can save time, risk, and cost by utilizing the primary container of their choice, whether vial, cartridge or prefilled syringe."

Enable Injections: Improved Subcutaneous Delivery for Large-Volume Injections

Successful delivery devices have the capability to make meaningful improvements to the patient and user experience, benefitting the user by simplifying drug delivery, improving usability, and reducing potential user errors. Enable Injection's enFuse® wearable delivery system is an innovative solution for patients to receive large-volume therapeutics subcutaneously. The enFuse elastomeric tech-

Engineering gets you off the blocks, ***but education gets you the WIN.***



Today's novel therapies and delivery devices call for innovatively engineered, cost-effective demonstration devices that support patients' needs. ***But that's just the starting point.***

For a successful start and long-term win, we deliver engaging, educational solutions that support the onboarding experience for patients, caregivers, and healthcare providers. Our proprietary approach to educational design and health literacy ***ensures certainty of use*** across the board—***so everyone gets the W.***

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Enable's enFuse® has the flexibility to deliver 5-25mL in a single on-body drug delivery solution.

nology delivers therapeutics at a low pressure, responsive to the pressure in the subcutaneous tissue and an elastomeric reservoir doubles as the pump and allows a delivery responsive to skin backpressure.

Jennifer Estep, Senior Director, Global Marketing & Commercial Strategy, Enable, says early clinical results give relative confidence that the unique design characteristics of enFuse may translate to potential clinical benefits and show an increase in patient preference over alternative current large-volume methods of subcutaneous delivery. In a separate 488-patient preference study that looked at SC trastuzumab, 90% of patients preferred SC administration over IV, and 80% explained time savings was the greatest benefit.[2] "Enable Injections' enFuse offers flexibility and time savings compared to traditional IV administration for both providers and patients," she says.

enFuse also allows a range of delivery from 5-25mL, and the needle is hidden the entire time the patient handles the device. A safety tab prevents premature button engagement, which keeps the needle hidden before injection. Once the user removes the safety tab and presses the button, the needle is hidden by the body. When treatment concludes, the button pops causing the needle to retract and lock into place, which ensures the needle is never exposed to the user.

For patients, the enFuse is discreet and can be worn under clothing and patients may go about normal activities while receiving an injection. Ms. Estep says: "New connected technologies such as the Enable Smart enFuse technology could potentially allow advanced injection data and remote monitoring for providers and caregivers."

Flex: Connected Solutions Can Improve Patient Compliance

The FDA increasingly has reinforced the importance of usability studies in medical device design to simplify device use, reduce error, and increase utility. As it relates to autoinjector device data collection, legacy Bluetooth connectivity is being replaced by newer technologies including low power wide area networks and narrow band Internet of Things, so dependence on intermediary equipment such as smartphones is eliminated, explains Jennifer Samproni, CTO, Health Solutions at Flex.

"In simpler devices, such as disposable prefilled syringes, there is a

growing need for remote patient monitoring solutions," she says. "This is achieved by adding an intelligence layer enabled by low-cost printed electronics and connectivity solutions."

Flex deploys internal product accelerator programs to stay ahead of medical market and technology trends such as these. One such program is its Smart Autoinjector Demo Platform, which interweaves technological advancements with simplification and user personalization. "Our goal is to create drug delivery platforms that are an extension of what the patient does naturally, factoring in grip, strength, eyesight, and composition of skin, all of which can change over time within the same user," says Ms. Samproni. A novel method is to make the interaction user friendly across the spectrum with voice recognition technologies, which Flex has integrated into its platform.

The platform emphasizes three critical themes to improve patient compliance:

Simplicity of use: This user-centered design philosophy focuses on designing a product experience that fits with user lifestyles, behaviors, and abilities. Interviews and observations, journey mapping, and ergonomic research provide user insights that are synthesized to establish foundational design tenants for the product. Simulation of physical and digital interfaces through use of virtual reality, tablets, and user experience models accelerate feedback at early stages and enhance quality of data, ensuring a strong design direction.

Information Relevancy: Timely sharing of personalized data has a positive impact on patient outcome, which is particularly important in chronic disease management. Empowering patients by providing customized information and clinical team support increases their self-awareness and drive to adhere to their treatment plan. Supported by cloud-based analytics, the monitoring system detects patient patterns and can provide reminders and statistics. Physicians can step in remotely to provide consultation and acknowledge good performance.

Reliability: Reliable performance requires a strong quality engineering commitment from the early design phases driven by a foundational design verification and device validation strategy. Flex's device platforms rely on advanced simulations upfront, such as radio frequency and antenna optimization for connectivity functions, comprehensive simulations for drive systems, tolerance and stress analysis for mechanical parts, and molding simulations for plastic parts. This is followed by extensive hardware and software device testing.

"Medical device engineers need to keep pace with changing dynamics in the healthcare industry, including frequently changing regulations and the need to reduce environmental impacts through sustainable design and materials across the product lifecycle," says Ms. Samproni. "At the same time, engineers must find the balance between user needs, cost, and time to market. This drives Flex to invest in solutions that make it easier for pharma companies to deliver compliant solutions with speed and confidence."

Gerresheimer: Devices Enable Large-Molecule Administration

Subcutaneous injection is becoming more relevant because it is generally preferred over the IV route of administration and reduces the burden and costs on the healthcare system. The need for subcutaneous drug administration is arising not only for

Gerresheimer's SensAIR technology can inject volumes up to 20mL.

small volumes, which could be applied through hand-held devices and pen/autoinjectors, but also for larger injection volumes, demanding more complex systems such as patchable or companion devices.

With a focus on the needs of patients and healthcare professionals for certain therapeutic areas such as oncology, immune system disorders and/or chronic diseases, the Gerresheimer device solutions are specifically tailored to fulfill the requirements of sensitive drug formulations such as biopharmaceuticals.

While Gerresheimer's autoinjector covers a range of injection volumes from 1.5-3mL using a glass cartridge-based design, the SensAIR technology is designed to address injection of larger volumes up to 10mL or even 20mL.

"Both concepts enable the administration of large molecule and biopharmaceuticals with different viscosities over a desired application time based on the requirements of the therapy and the drug in question," says Reza Abedian, PhD, Senior Medical Affairs Manager, Gerresheimer.

Targeted users and relevant stakeholders of these devices, including patients and healthcare professionals, were involved in the design and development process of these devices. Dr. Abedian explains that surveys of patients with cancer, immune system disorders, and metabolic diseases, as well as learnings from interviews with clinicians and nurses, drove the device design.

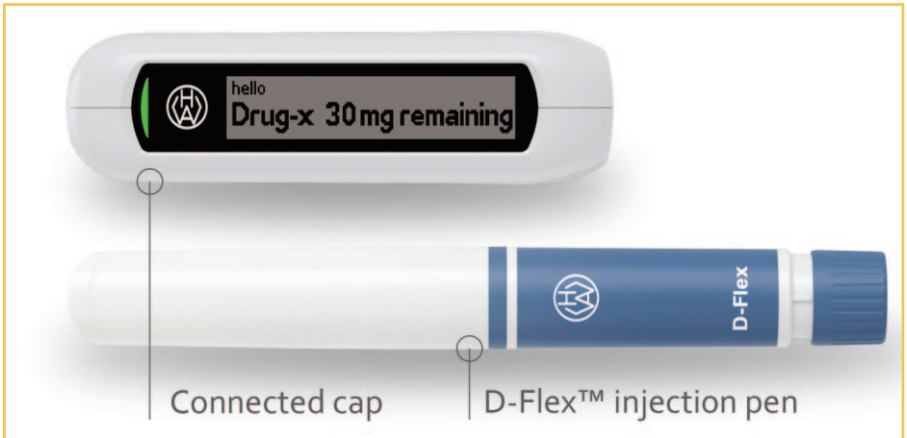
Haselmeier: Injection Pen & App Impact Patient Behavior During Trials

Haselmeier, the drug delivery division of medmix, introduces the D-Flex Logbook, which complements patients´ self-injection from clinical testing to commercial launch. Frank Leipold, Vice President Product & Portfolio Management at Haselmeier, explains why the D-Flex Logbook is key to more transparency in clinical trials and how it adds tangible value during clinical testing of new drugs.

The success of clinical trials with self-injection devices relies on patient compliance. While many patients comply with their therapy, others might not or only in part. "Until now, there are only limited possibilities to check the extent of patients' real adherence to the prescribed therapy. Clinicians mostly rely on patients' feedback," Mr. Leipold says. And that is one of the reasons why wearables and connected devices are increasingly finding their way into clinical trials.

In order to make clinical studies with self-injection devices more transparent, Haselmeier developed the D-Flex Ecosystem in 2020. This real-time solution enables stakeholders, like clinical research organizations, to quickly utilize real-world evidence to impact patient behavior during an ongoing trial. However, this kind of ecosystem usually depends on a patients' access to a mobile phone, either their own or an additional one provided by the investigator. Additional devices increase operational and regulatory efforts and increase overall cost of clinical testing. This is why Haselmeier developed the D-Flex Logbook, which collects injection data at the point of care without the need for a patient mobile app.

The D-Flex Logbook consists of the disposable D-Flex injection pen and the connected cap, which replaces the standard cap of the pen. Patients remove the connected cap from the injection pen, dial a dose, self-inject, and put the cap back on the pen; exactly how they would use a pen and a standard protective cap. Once the patient returns the cap onto the pen, the connected cap automatically identifies the administered dose, the current temperature and time, and stores this injection event in its internal memory. The cap can store up to



The connected cap on the D-Flex Logbook collects injection data at the point of care and can store up to 1,000 injection events (Haselmeier).

1,000 injection events.

These events can then be retrieved by study nurses or clinicians at each patients' site visit to identify and address issues with patients during the ongoing trial. This additional information supports the interaction with patients during the on-going trial and should help to improve patient behavior.

The most important benefit of both systems, the D-Flex Logbook and the D-Flex Ecosystem, is that they allow evaluation of the legitimacy of each patients' outcome data. "Without such a system, patient data from non-adherent patients or incorrectly stored injection pens would dilute the efficacy level of the outcome data of adherent patients, says Mr. Leipold.

In summary, he says the D-Flex Logbook provides paper-free numerical evidence for each patient, allowing study sponsors to evaluate adverse events and to exclude certain patients´ data based on real-world evidence, which should positively impact clinical outcomes of newly tested drugs.

ICON plc: Empowering the Patient

The inaccessibility of office visits and the need for social distancing at the height of the pandemic led many to begin administering their own medications via injections, accelerating previous upward trends of self-injection utilization and technologies. With a wide variety of wearables, autoinjectors, pens and even needle-free drug delivery devices in development, for many, this practice represents the patient's ability to play an enhanced and active role in their own healthcare.

However, self-administered injection comes with its own set of patient needs and risks. These factors are informing the development of smart injection technologies and features. One of the most critical metrics for self-injectable medications is the ability for the patient to track doses. "Without adherence to a treatment plan, patients will lose the medical efficacy of self-administered injectable medications," says Dr. Devin Ridgely, Director, Project Management, Medical Device & Diagnostics Research, ICON plc. "Forgetting doses is a prominent problem for many patients — particularly those for whom injections are so routine that it is easy to lose track of time and frequency of administration."

To combat patient "forgetfulness," many injection devices are utilize Bluetooth capabilities to transmit administration data to an app on the user's phone. Smart devices can provide reminders at the appropriate time or alert the patient when a dose has been missed.

Similarly, the use of smart technology can be harnessed to reduce user error. Medications that require frequent injections increase the probability for user error, which impacts the efficacy of the treatment and overall patient health. Some connected devices offer guidance through the injection process and can detect errors, such as holding time, during administration. Other metrics that can be tracked are drug expiration dates or if the drug had a damaging temperature excursion, rendering the drug unusable/unsafe for self-administration.

"Digitally connected wearable injection devices can empower patients by helping them control their comfort and treatment plan in accordance with physician recommendations," says Dr. Ridgley. "A variety of possibilities for smart device connectivity and feedback communications is well positioned to meet the needs of patients. As capabilities grow, clinical applications will expand, and developers will continue to adapt new features and functionality to improve the lives of those who choose to self-administer injections."

Kahle Automation: Designing Automation That Produces Complex Devices

As home health care becomes more essential and more drugs are finding homes in wearable devices, the automation equipment for manufacturing these devices becomes more essential to meet the demands of the market. Manufacturing these complex medical devices is a challenge. The critical dimensions and performance of the devices require an automation partner that understands these constraints and provides a custom solution to meet these requirements. Working with companies from the early stages of a project allows both the product and the automation design to develop together to meet the initial production needs and the long-term high-speed manufacturing requirements with robust, proven designs.

"The biggest concern that needs to be addressed is that failure of a de-

Kahle Micro Component Assembly System – 450ppm.

vice in the field is not an option," says Julie Logothetis, President, Kahle Automation. "The biggest challenge to manufacture these devices, as components are becoming smaller and smaller, is the need to feed and assemble along with 100% inspection of the assemblies as part of the manufacturing process."

Kahle has a portfolio of designs and process solutions for the assembly and packaging of most medical devices and pharma products. Beyond creating an assembly system, Kahle validates the system and transitions the equipment into production.

"When choosing an automation partner, consider the breadth of experience a potential partner has in handling processes and parts of similar size, the flexibility of their design process to think out of the box, and the capability to evaluate process risk coupled with mitigating that risk by verifying concepts up front in a proof of principle or design of experiment," says Ms. Logothetis. "An automation partner should be solution focused and have demonstratable experience and reputation in the medical and pharmaceutical industry to ensure innovative, robust, timely, and cost-effective results."

Nemera: Simple & Sustainable Design

The on-body injector platform, Symbioze®, administers complex, large-volume drugs, such as monoclonal antibodies. Features include an adjustable flowrate to fit patient and drug administration profiles, near-field communications recognize the drug and verifies injection, built-in Bluetooth enables connectivity, and a reusable electronic part and disposable module.

"By offering reusable parts for multiple use, we are addressing the need for integrating sustainability into design," says Cécile Gross, Global Category Manager, Parenteral, Nemera.

In addition to sustainable design, Ms. Gross says injection devices must maintain their ease of usability. "Simplicity of injection with a robust advanced delivery system prevents overcomplicating usage and doesn't compromise the patient's experience," says Audrey Chandra, Category Project Manager, Nemera.

Symbioze addresses this need as it is ready-to-use prefilled and preloaded with a large-volume cartridge (up to 20mL), designed for patients with chronic conditions, such as Rheumatoid arthritis, psoriasis, and multiple sclerosis. "These patients require lifelong medication that enhances comfort to manage their treatment," says Ms. Chandra. "This is particularly important when self-administering complex, large-volume high-value biologic drugs, such as monoclonal antibodies."

Nermera's Symbioze® is a smart and sustainable on-body injector platform to improve patients' injection experience.

Oval Medical Technologies ltd.: An Autoinjector Platform Designed for Home Use

The current trend of treatments moving from hospital to home and towards longer acting formulations have the potential to produce an improved experience for patients, with the increased convenience of fewer visits to treatment facilities and less frequent injections. However, with this transfer of treatment to the patient's control, there is the potential for an additional burden on patients. Longer injection times and a lack of device familiarity due to infrequent injections means that delivering each injection can end up being as daunting as the first, says Barbara Lead CEO Oval Medical Technologies ltd.

"This new context of use, which can lead to injections becoming a challenging, stressful experience for patients, represents a specific set of user needs that must be addressed through careful, considerate design," she explains.

Oval has developed ArQ-Bios, a customizable subcutaneous platform with options for both high viscosity and large-volume formulations to cater to this set of user and delivery needs. Developed with home use in mind, it provides a package that enables patients to self-administer a range of formulations that could prove challenging both from the standpoint of device capabilities and patient experience. Key features include Oval's proprietary valve design, which allows delivery-spring release to be decoupled from actuation, leading to a gentle start of injection, with no shock from a large release of energy on actuation. As delivery progresses, the user is further supported by a 360-degree window, giving clear visibility of delivery progression from whatever angle the patient finds comfortable, removing uncertainty and worries about receiving the full dose, Ms. Lead describes.

"Throughout the user interface, every element has been carefully considered, with potential false cues and confusing elements avoided, and design inspiration taken from consumer trends giving the patient a device that feels more at home in their environment, rather than something that looks like it's been taken straight from a hospital," she says. "The user interface of ArQ-Bios has been developed with a core focus on usability, with elements tailored to make the injection experience simple, repeatable and stress-free in home use contexts.

Owen Mumford Pharmaceutical Services: Autoinjector Accommodates Syringe Sizes, Volumes & Viscosities

Owen Mumford Pharmaceutical Service's Aidaptus® is a simple, two-step, single-use autoinjector platform designed for the treatment of patients who require subcutaneous medication as part of their chronic disease management. Michael Earl, Director, Pharmaceutical Services, Owen Mumford Pharmaceutical Services, says that a human factors program demonstrated that Aidaptus can be successfully used by a range of patients with varying conditions and demographics, as well as by healthcare providers. Aidaptus can be used with both 1mL and 2.25mL syringes in the same device and accommodates a variety of fill volumes and viscosities using unique auto-adjust plunger technology and a choice of two strengths of delivery springs. The design also helps to mitigate breaks in container closure integrity (CCI) by limiting rearward movement of the stopper.

"This means the same device can be used regardless of formulation changes, which can occur in development and on through product lifecycle management," he says. "It also mini-

Aidaptus® two-step, single-use, autoinjector platform from Owen Mumford Pharmaceutical Services.

mizes some of the additional work required for the development of multiple combination products such as validation testing, human factors studies, and regulatory submissions as well as the need for new final assembly equipment. With Aidaptus, if a pharma company's formulation changes, the delivery device does not."

Owen Mumford Pharmaceutical Services is collaborating with Stevanato Group on the manufacture and commercialization of Aidaptus. Stevanato Group will provide molded components and assembly equipment and is a partner in the capacity scale up and commercial roll-out for the device.

The Aria Smart Autoinjector offers a simple user interface that provides audio and visual feedback that an injection is complete (Phillips-Medisize).

Phillips-Medisize: Mechanical & Electronics Combined Into One Autoinjector

The Aria Smart Autoinjector being developed by Phillips-Medisize is an example of combining the benefits of existing mechanical devices with new features that are realized through use of electronic devices. A basic version of the device provides a user experience comparable to that of a disposable mechanical device, with a simple user interface providing visual and audible feedback throughout; notifying when the injection is complete, avoiding the need for patients to count, explains Iain Simpson, Director, Front End Innovation, Phillips-Medisize. An advanced version, Aria+, includes a graphical interface that can support more complex drug delivery, such as partial dosing from a syringe or the use of multiple cassettes to deliver larger-volume doses. It allows adjustment of injection speed and the use of animation to provide training support.

"Compared to a spring-based system, Aria ensures gentle engagement with the syringe/stopper while delivery force is automatically adjusted to maintain a constant speed throughout," says Mr. Simpson. "This reduces the risk of syringe breakage and shear damage to the drug, allowing optimization for a range of drugs, particularly emerging complex biologics."

Patient compliance relies on minimal user burden and clear feedback to reduce use errors. Aria's simple sleeve-triggered activation and large inspection window provide commonality to current single-use devices, meaning a familiar configuration for established autoinjector users and a non-intimidating experience for naïve patients, he says. Supporting companion digital services enable better patient support via an app or through remote healthcare professional support with real-time use data.

"Data from marketed electronic autoinjectors is providing evidence that adherence can be improved through smart autoinjectors," he says. "Emerging needs around sustainability, connectivity supporting companion digital services, and flexibility around drug volume and viscosity are creating opportunities for electronic reusable autoinjectors."

Mr. Simpson points out that Phillips-Medisize is collaborating with

a pharma customer to provide a highly viscous drug that could only be delivered using a mechanical autoinjector or prefilled syringe with a much larger needle. Another customer is assessing partial dosing from a prefilled syringe to increase dosing flexibility, enabling dose titration and reducing the number of prefilled syringe SKUs required to support weight-based dosing for a broad population.

Portal: Needle-free Platform is Designed to Deliver High-Viscosity Drugs

The CDC estimates 25% of adults have a fear of needles, cites Portal. Because these fears are triggered by the presence of a needle, no easy solution to the problem exists beyond helping patients relax or avoiding injection altogether. Patients may have to accept a medication with reluctance, need someone else to administer it for them, or seek non-injectable therapies that may require more frequent dosing, dietary restrictions or a greater risk of serious adverse events.

"The lack of enthusiasm that arises from having only suboptimal device options may increase the risk of poor adherence and poor persistence on therapy," says Patrick Anquetil, CEO, Portal. "By providing a better experience via the needle-free injector, and with its connectivity features including reminders and sharing of real-time injection data, Portal is looking to improve compliance."

Portal is developing a needle-free injector that can handle volumes up to 2mL at high viscosities of up to 60cP in less than .6 seconds. Rick Smith, Senior Vice President of Strategy, Portal, explains that typical biologic concentrations are ≤200 mg/mL. "With increased dose needs, there becomes a trade-off between concentration, which leads to higher drug volume or to higher viscosity. New drug delivery systems are needed to handle high viscosity drugs or higher volumes in a patient-acceptable format."

The Portal device is designed to be easy to use by the patient and can be connected to patient apps or a wellness team to provide a more complete data picture. "As more patients consult with their care team from a distance, there is a need for objective information, such as dose adherence, that can feed automatically into the patient's digital record," Mr. Anquetil says.

Portal's PRIME needle-free platform is designed to deliver medications with viscosities of up to 60cP and volumes up to 2mL in .6 seconds.

Portal's needle-free injector is well-suited for patients with a chronic disease, who need to take subcutaneous injections on a regular basis, often at home. "The drive to divert more care to home as a lower-cost care setting has led to the need for more patients to be able to self-treat and self-inject at home. Meanwhile, the trend of more medical devices being used in the home is converging with the trend of more consumer devices looking like medical devices (wellness apps, watches). This is creating an expectation for medical devices to be as easy to use and connected like their consumer electronics and wellness tools."

Stevanato Group: Platform Device Balances Ease of Use With Design

Platform injection devices are an off-the-shelf option that can be customized for a variety of drugs and primary packaging with minimal change components, compared to bespoke devices, which can be a huge upfront investment, says Adam Stops, Head of Product Management for Drug Delivery Systems, Stevanato Group. "Platform injection devices keep costs down and offers faster time to market, enabling patients to benefit from new

therapies sooner rather than later."

Reducing the complexity of the supply chain is also part of the device design process, he says, affecting everything from the components to the assembly procedures. Sustainability is a key factor and the supply chain for the raw materials has to be robust. "Guarantee of supply has become crucial in the wake of the disruption seen during the pandemic," he says.

Integration is another source of innovation in injection device design to ensure devices are ready to be a combination product through integration with prefilled syringes or cartridges and manufacturing processes such as fill-finish techniques. "With such compatibility built in, the latest platform devices reduce risk and speed up time to market," says Mr. Stops.

The SG Alina® is an example of integration. Stevanato Group designed the disposable pen-injector platform to be fully compatible with the company's range of glass cartridges and final assembly equipment sold to customers. "This helps to ensure a robust device and dosing consistency for patients," says Mr. Stops. "Designing the device to better fit the entire ecosystem and variability in user functions – such as dose delivery force, dose selection, and dose accuracy – help to make a difference when it comes to patient compliance."

SG Alina is designed for variable and multi-dose treatments for conditions such as diabetes and obesity. A user-friendly, ergonomic design includes an easy-to-dial dose mechanism with an intuitive display, as well as optimized injection force for patient comfort, says Mr. Stops. Clear pre-injection dose indication is designed to avoid under dosing, with only one number visible in the dosing window at any given time to reduce the possibility of confusion; a dial-back enables dose correction. Patients also receive visual, audible and tactile feedback for dose setting, correction and injection.

A range of customization options is available for different primary packaging and therapy needs.

Individual colors can be selected, for example, for different types of insulin to help avoid patient confusion and boost compliance. And the size and position of labels, as well as the printed information itself, can be tailored according to pharma companies' requirements.

Mr. Stops says: "SG Alina is designed to strike the right balance between pharma companies' desire for innovation in product design and the need for familiarity to encourage patients to use a new injection device successfully."

Vetter: Realizing Patient-Centric Devices

As a CDMO, Vetter is not only aware of what injection devices are on the market but also the differences that exist between them. This helps to create the relevant capabilities for the assembly and packaging of device systems, says Markus Hörburger, Product & Service Manager, Vetter Pharma International GmbH.

He says it is important that Vetter considers user-friendly device systems as well as the processability of the device to support successful market launches. "Our deep expertise and capabilities help our customers in realizing their patient-centric devices," he says. "It is expected that COVID-19 will further accelerate this market shift and increase demand for home-care applications."

Mr. Hörburger adds that patients expect a simple, safe, intuitive delivery experience that supports adherence. Thus, various delivery device designs are addressing the need to increase

Vetter creates the relevant capabilities for the assembly and packaging of injection device systems.

injection convenience. Within this context, there is also a trend toward health insurance organizations placing a greater emphasis on understanding if a drug was taken by the patient as prescribed and if it was effective. The biopharmaceutical industry is adapting to these trends by leveraging new digital solutions such as smart labels and connected devices.

West Pharmaceutical Services: Bringing Sensitive Molecules to Market in Larger Autoinjectors

With the shift of care into the hands of the patient comes the need for intuitive ergonomic design, simplicity, and the highest quality at every touch point to achieve a reliable, safe administration of the full prescribed dose. The Crystal Zenith® (CZ) 2.25mL insert needle syringe system is one such containment solution that protects sensitive molecules that are administered by an autoinjector. It is free of tungsten and glue, does not have added silicone oil added for functionality, and reduces the worry of container breakage during high-force, larger-volume injections.

"The availability of larger-volume autoinjectors, such as those which contain a 2.25mL prefilled syringe, enable patients to use a single injection per dose," explains Dr. Nicolas Brandes, Director, Product Management, Vial Containment & PFS, West Pharmaceutical Services. "Larger volume injections are not only well accepted by patients, but it is those patient groups advocating for, and driving, change towards more choice around treatment management. West's CZ 2.25mL insert needle syringe system will play a pivotal part in bringing sensitive molecules to market in larger autoinjectors."

Modern biologics, such as proteins and monoclonal antibodies, exert demanding requirements on their containment system, which can be difficult for drug developers to navigate if a platform approach to packaging has been used in the past. This platform approach failed one of West's customers, because they experienced expensive project delays when they selected their "tried and tested" large-volume, glass syringe system to package a drug to be used in an autoinjector for self-administration.

Victoria Morgan, Director, Segment Marketing, Global Biologics, West Pharmaceutical Systems, says the formulation development team picked their platform glass syringe system to package their new biologic drug in development, yet subsequent time pulls of stability samples showed the drug was silicone sensitive which, in turn, made the drug unstable. Analytical testing showed the presence of both visible silicone and protein in the drug product forcing the formulation team to reassess the primary packaging system.

"The biologic molecule required a prefilled syringe system with as low silicone oil as possible to maintain drug stability, which included both the syringe barrel and drug facing surface of the plunger," she says. "In addition, the new containment system was expected to perform as well as a glass system with respect to functionality, which includes break loose, extrusion, and gliding forces, injection force, rigid needle shield removal force, and container closure integrity.

These were critical performance factors as the prefilled syringe system would be used within an autoinjector for the final drug delivery system."

The customer assessed the market for a suitable syringe system and selected West's Crystal Zenith (CZ) 2.25mL insert needle syringe system; the barrel of which doesn't have silicone oil added for functionality, and the drug facing end of the plunger utilizes Flurotec™ barrier film for lubricity and offering a low extractables and leachables profile. Ms. Morgan says the drug was stable in the CZ syringe system and the customer was able to show better results for sub-visible particles with CZ than with glass and other polymers.

Ypsomed: Targeting Subcutaneous Delivery of Large-Volume Drugs

Demand for new device innovations for subcutaneously delivered drugs has been dominated by the need to inject larger volume injections. This has spawned demand for larger volume handheld autoinjectors and a new device class of patch injectors that adhere to the skin during injection. With regard to this development, Ypsomed offers the family of YpsoMate™ autoinjectors and the YpsoDose® patch injector.

To simplify the administration of new mAb-based cancer therapies, many of the currently approved drugs or drugs under development are targeting subcutaneous (SC) delivery.

Ypsomed's YpsoMate 2.25 Pro autoinjector with constant force spring technology for the delivery of viscous drugs.

"Treating cancer, particularly during the initial stages that require surgery, radiation, and chemotherapy as well as immuno-oncology, will always be performed in the hospital environment," says Ian Thompson, Vice President Business Development, Ypsomed. "But, even in the clinical setting there are advantages of replacing IV infusion regimens with more convenient, easy-to-prepare and administer SC therapies. Following a successful first phase of treatment that forces the cancer into remission, there will be significant demand for injectable maintenance therapies to be performed in the hospital and ultimately in the home environment."

Ypsomed has developed and industrialized the handheld YpsoMate 2.25mL in two versions (standard and Pro for more viscous drugs) and the YpsoDose 10mL patch injector for large-volume SC injections. Moreover, Ypsomed is expanding the design space for rapid handheld high-volume injections. Both types of device are used for therapies that dose every week, two weeks, monthly or even less frequently. "The number of use steps and complexity must be minimized to ensure that all users will remember the correct handling even with a longer timespan between injections," says Mr. Thompson. "Accordingly, simplicity and safety are key requirements for both autoinjectors and patch injectors."

The 2-step YpsoMate autoinjector is triggered by push-on-skin activation, requiring two steps: remove cap and inject. The same approach is applied to YpsoDose, in which case the two steps are: patch and inject. YpsoDose is an electromechanical device with a digital user interface that ensures clear and unambiguous communication of the device status to the user, says Mr. Thompson. The integrated skin-sensing patch guarantees needle safety even in case of user errors, such as early activation of the start button or premature removal of the device from the skin.

The YpsoMate 2.25 Pro, with 2-step handling, is designed with a constant-force spring to allow reliable and reproducible injection of drug viscosities in excess of 15-20cp at room temperature.

SHL Medical: Integrating Transparency in Connected Self-Injection Devices

In the present healthcare landscape, novelty in drug delivery means self-injection systems that open pathways toward better treatment journeys for patients. Influenced in recent years, biopharma is consistently expected to prove value and effectiveness pre- and post-regulatory approvals. This means that evidence needs to be effectively communicated throughout the health ecosystem – from the payers and pharmacy benefit managers to the regulators and health authorities and so on. Connectivity requirements are now more than ever focusing on the value beyond the patient. In this context, the main intent of connectivity is to collect up-to-date research and development data as well as treatment related data and consequently, have a better understanding of the treatment process and its real-world effectiveness. Connectivity allows further refinement of the patient experience and ultimately improves treatment outcomes.

Over the years, various factors stemming from patients and treatment providers have influenced the evolution of injector device designs and their functionalities. For one, ensuring patient safety by preventing common medication errors has been an ever-present driver. "As the self-efficacy of chronic disease patients continues to increase, connected self-injection devices not only support safety of the administration process, ensuring that the right dose is taken at the right time," says Nils Weber, Global Head of

A synergistic partnership between SHL Medical and Innovation Zed gave rise to InsulCheck DOSE, a connected add-on device for automated logging of injection information.

Emerging Technologies and Digital Health at SHL Medical. "This symbiotic relationship between connectivity and increased treatment adherence is extremely important in cases where dose accuracy is vital, such as in stricter or complex medication regimens like diabetes."

SHL Medical designs and develops self-injection devices like autoinjectors and pen injectors. With its pharmaceutical partners, the company co-develops combination products for chronic diseases like Rheumatoid Arthritis, multiple sclerosis, atopic disorders, as well as diabetes. "In realizing better-connected healthcare, SHL's digital health ecosystem builds from our innovation partnership framework to support the connectivity journey of its global pharmaceutical partners and their self-injection products," he says. "This digital health ecosystem extends beyond the end-user device to better enable data ingestion for the optimization of therapies."

SHL understands that integrating transparency in connected self-injection devices is key to simplifying the adherence challenges faced today. With the decentralization of treatment-related data – which allows patients transparent access to injection event data, big data analysis, as well as convenient device (fleet management) control – connected device technologies can ultimately facilitate patient adherence. Through a partnership with Innovation Zed, SHL has led digital health explorations in co-developing smart add-ons for pen injectors. The culmination from this partnership resulted in the 2022 commercialization of InsulCheck DOSE, a third-generation connected add-on that supports the monitoring of disease management regimens. InsulCheck DOSE by Innovation Zed is a Bluetooth®-powered device that transforms the traditional injection pen into a smart pen, allowing for the automated logging of injection information. In chronic disease treatment scenarios, the add-on device utilizes an OLED screen that displays the time elapsed since the last injection, shows the last dose unit, as well as indicates mounting/unmounting activities. Data from the device can be sent to a third-party software application for automated logging of injection information, which the patients can access.

"Together with our partners at SHL, we have developed a built-in firmware over-the-air (FOTA) capability for InsulCheck DOSE, which allows continuous optimization of the device's firmware even when deployed in the field," explains Dean Minnock, Chief Executive Officer at Innovation Zed.

"There is an untapped potential in the field of home-based treatment for connected autoinjectors," says Mr. Weber. "With the device as an integral component of our digital health framework, together with our pharmaceutical partners, we are actively exploring connected solutions for both the clinical and commercial phases of their development projects." These connected solutions support decentralized clinical trials, automated, real-

life, and central data collection, increased data accuracy, as well as increased patient adherence with the ultimate goal of improving patient outcomes.

Duoject Medical Systems: Custom Solutions for Today's Patient Needs

For novel drugs (as opposed to generics) there is a clear move of pharmaceutical companies towards combination devices that adapt to more complex drug requirements; i.e. specific volumes, higher viscosities, more challenging drug stability. This means that off-the-shelf device solutions increasingly require customization; while in many instances, brand new device systems are required altogether, says William Fortina, Business Development Director, Duoject Medical Systems.

He adds that there is also an increased demand for patient convenience, which translates into home-care options, self-administration with fewer and simpler user steps, and less frequent dosages. "These trends make the job increasingly challenging for device designers and producers who must simplify the user experience, while having more challenging technical requirements, and the ever-present need to control device-related costs," says Mr. Fortina.

Duoject Medical Systems develops injection, drug reconstitution, and safety systems. Mr. Fortina says that the company has received an increasing number of enquiries in recent years for combination devices that can perform both drug mixing/reconstitution/resuspension, as well as drug injection within the same device. He says: "As a result of our client's formulations each having their own unique requirements, we have been working on different custom solutions, based on and leveraging various existing Duoject IP. The solutions we are developing for our clients will allow convenient at-home administration for complex or unstable drug formulations, through simple and intuitive mechanisms. Simplifying the device's operation for patients improves compliance as they are more likely to use a device that is intuitive and safe to handle." ◆

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DRUG DEVELOPMENT STRATEGIES

Marrying Target Product Profile, Regulatory & Partnering Strategies for Long-Term Product Success

By: Chris Rojewski

INTRODUCTION

Drug sponsors and intellectual property (IP) owners understand how critically important it is to establish the target product profile (TPP) of the proposed drug product as early as possible. The TPP provides regulators with a summary of the prospective drug development program and its drug labeling objectives. It is also the key to determining the product's eventual commercial formulation.

Essentially a map of drug strategy, the TPP can be a helpful navigation aid describing desired product and formulation attributes and the means to communicate them to all stakeholders, from IP owners, developers, and manufacturers to regulators.

Because it is such an important guide and a predictor of product success, it is just common sense best practice calls for developing a strong, realistic TPP to launch the program effectively. However, taking the conceptual product (described in the TPP) from lab to patient, especially if it includes external development and manufacturing partners, demands a regulatory strategy and a Regulatory Affairs (RA) response equally as strong.

PLAN FOR PROGRAM SUCCESS WITH A STRONG TPP STRATEGY

When launching any drug development program, it is essential all involved have a clear idea of why the proposed formulation and finished form are improvements over an existing drug product or best-class alternatives to currently available products or drugs in the development pipeline.

The TPP should be developed with the commercial objectives of the product in mind from the very beginning. To better reflect the product's eventual commercial reality, those objectives should be weighed against the drug's pharmacology as well as the practical necessities associated with most clinical development programs. The end goal is to generate a TPP that describes an optimized but market-realistic view of a drug's development goals.

Because the TPP must do a good job of predicting a proposed drug's future state, it needs a development strategy of its own. To sharpen the focus of the TPP's crystal ball, best practice calls for developing of the following three product descriptions initially:

1. Weak. A worst case minimally compliant product description.
2. Acceptable. A likely case that describes the middle ground somewhere between these best and worst case options.
3. Strong. The best case; what an IP owner is seeking to claim on the final label.

The Strong option is the primary objective of the TPP development strategy.

ENTER REGULATORY PARTNERING STRATEGY TO MANAGE PROGRAM RISK END-TO-END

An effective regulatory strategy serves to align a proposed clinical development plan with business objectives — generally aimed at worldwide distribution. The strategy also helps identify any potential challenges as well as solutions and alternative approaches to new product development. Additionally, the intent

and purpose of a robust regulatory strategy is to use it to fully develop a drug's TPP in an effort to broaden distribution globally and increase patient access.

A fundamental part of any drug commercialization strategy requires analyzing it for the regulatory risks the program may present. This is followed by instituting steps to manage and mitigate risks efficiently at every step so as not to interrupt or slow the program or increase development costs beyond a financially sustainable point.

RA departments understand that a strong regulatory strategy is earmarked by a common set of principles:

- Anticipatory
- Identifies/quantifies risks
- Forward and backward thinking
- Regionally, globally agnostic

Equipped with a strong, optimized TPP, IP owners, and often their contract partners, can begin to plan and launch the program it lays out. Because most aspects of drug strategy are associated with market-specific compliance, a purpose-built regulatory strategy supporting those objectives is essential to a drug product's commercial success.

DEMAND FOR EXTERNAL RA SERVICES LIKELY TO RISE

Much of pharma is turning to external contract development and manufacturing partners (CDMOs) to develop, manufacture, and commercialize their drugs.[1] Analysts expect the global market for CMOs and CDMOs to double by 2025, representing nearly $163 billion in value.[2]

From a drug developer's perspective, analyzing and managing the regulatory risk relative to their product and formulation is best left to experts, most often RA consultants or similar specialized resources within larger pharma companies. But the landscape is shifting, and with much of pharma discovery coming from small, virtual, and mid size companies developing drugs in early clinical phases, there will be increasing demand for external RA services to develop and execute regulatory strategy.

From a CDMO's perspective, IP owners with products under development often "tack on" regulatory strategy developed by third parties. This certainly has worked for a vast majority of drug developers, but just not as efficiently and cost effectively as it could or should be. Pharma needs access to a better RA solution, one that is engineered to meet the specific needs of the drug's commercial strategy and can proliferate throughout a product's lifecycle. Because a significant majority of pharma's developers are turning to CDMOs for commercial formulation and manufacturing, these prevailing business models suggest the best source to secure a cohesive regulatory strategy is from those partners.

CONTRACT RA SERVICE OFFERINGS EVOLVING TO MEET PHARMA'S PRESSING NEED

Across the space, CDMOs have historically been a source of regulatory strategy, mostly focused on the more technical aspects of technology transfer, commercial-scale formulation, and other essentials of compliant manufacturing. To a certain extent, most CDMOs offer RA services to support client programs, but not necessarily strategically and comprehensively enough to meet the expanding needs of pharma's "developer-class" of companies.

However, CDMOs certainly are not standing still and are beginning to recognize regulatory strategy is the "secret sauce" of successful commercial development. It should be no surprise then that progressive CDMOs are beginning to shape service offerings to provide the end-to-end regulatory strategy every drug needs to reach patients.

Breaking it down, a comprehensive service offering from the CDMO sector is likely to include strategy, submission, authoring, publication of submission, lifecycle management, and market expansion support.

It should create primary deliverables for Phase 1, including documentation required for all CTD Modules (1-5).

Ultimately an end-to-end regulatory strategy service offering provides an RA consultancy and a regulatory strategy more closely associated with the objectives (detailed in the TPP) of the product under development.

ASSESS CDMO RA POTENTIAL WITH PRECISION

When assessing the strategic potential of the RA service offering, sponsors should seek answers from the provider to key questions, such as the following:

- Does the prospective CDMO have a fully integrated and dedicated RA function?
- Does this RA team have the experience to address early development RA strategic needs including CMC risk mitigation?
- Can the potential CDMO fully publish a partner's regulatory submission in a secure and compliant manner?
- If needed, can the CDMO's RA team act on the partner's behalf, either in submitting applications to regulatory agencies or speaking on their behalf?
- Is the CDMO responsive? Can it respond efficiently and effectively to regulatory inquiries, when needed?
- As part of the service offering, does the CDMO provide lifecycle management support for your regulatory submission?
- Within existing infrastructure can the CDMO support global market expansion and renewal needs?

If most of the aforementioned questions are answered in the affirmative, it is more likely the value the benefits of the services delivered will outweigh the costs and at a price more affordable than hiring a separate consultancy.

REGULATORY STRATEGY DRIVES DRUG STRATEGY & VICE VERSA

To meet the objectives and goals of the TPP, to launch the drug strategy, and put it to work in development, requires a strong comprehensive end-to-end regulatory strategy. More than that, it is essential to efficient program execution, from early development to commercial manufacture, as well as long-term lifecycle management.

Pharma's innovators are relying on CDMOs for more services and deliverables than ever before, as well as expertise. Given the costs, time, and risks associated with contemporary drug development, it's time this fundamental aspect of successful development be brought as close to the program as possible — the CDMO tasked with executing drug strategy in the first place. ◆

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BIOGRAPHY

Chris Rojewski has more than a decade of expertise in regulatory affairs and more than 28 years of experience in the pharmaceutical industry. After earning his BSc in Chemistry from the University of Iowa, he began his career as an Analytical Chemist at Abbott Laboratories, later joining Pfizer in 2016. With extensive experience in chemistry, manufacturing, and controls, he now expertly manages Pfizer CentreOne's Regulatory Affairs team as Director and Team Lead in Global Regulatory Affairs.

LIVE BIOTHERAPEUTIC PRODUCTS

Not All Microbiome Approaches Are Created Equal

By: Duncan Peyton

INTRODUCTION

The microbiome is the complex ecosystem of microorganisms that live on and in the human body, including bacteria, fungi, archaea, and viruses. Weighing around 2 kg and estimated to contain around 100 trillion bacterial cells representing thousands of species, bacteria in the human gut microbiome outnumber human cells in the body.

All this material is home to vast genetic diversity and functional output. The estimated 2 million bacterial genes in the average human body dwarfs the approximately 20,000 protein-coding human genes. This genetic abundance and breadth, but more importantly its outputs, represent a vast and rich pool of functionality, already optimized by evolution to impact human pathways, and to be leveraged for therapeutic effect.

THE MICROBIOME: DIFFERING APPROACHES TO A NEW MODALITY

The microbiome is a rapidly maturing area of research, and multiple companies are pursuing various strategies to exploit the microbiome for therapeutic benefit. While these strategies are rooted in the same source, they diverge significantly in terms of scientific thesis, proposed mode of action, and development complexity.

Live Biotherapeutic Products (LBPs) are a recognized class of drug, defined by the US FDA as "a biological product that contains live organisms, such as bacteria, that is applicable to the prevention, treatment, or cure of a disease or condition of human beings, and is not a vaccine." This is an important distinction from both fecal material transplant procedure and small molecule or biologic drugs also derived from the microbiome.

Within the broad umbrella of "microbiome therapeutics," distinct schools of thought have emerged regarding how best to tap into the microbiome for therapeutic applications. Different rationale often underlies the different approaches taken in microbiome research and has implications for drug development.

Recent years have seen rapid maturation of the microbiome therapeutic landscape, with numerous drug candidates representing a range of approaches in clinical studies for a wide variety of diseases. This has been assisted by an evolution in the way companies are thinking about the microbiome and LBPs as pharmacological agents. A closer examination of the various approaches helps define the microbiome space.

FECAL MICROBIOTA FOR TRANSPLANTATION (FMT)

FMT involves the transfer of a sample of the microbiota from a donor into the gastrointestinal (GI) tract of a recipient, to repopulate the recipient's "dysbiotic" microbiome. This typically involves antibiotic pretreatment of the recipient to remove the resident microbiota. FMT is the most basic form of microbiome therapy, in which the entire microbiome is transferred wholesale in an attempt to recreate a specific microbiome signature that is associated with a healthy state. Screening of the fecal material is required to identify pathogens, but otherwise the microbial composition of the material is not actively modified in any significant way.

FMT is considered by the FDA to be a procedure and not a drug product. It has proven successful for preventing recurrence of GI infections such as Clostridium difficile (*C. diff*). FMTs are also now being tested in clinical studies for a wide range of conditions from cancer to autism; however, such studies are often open-label and poorly controlled and therefore unlikely to provide conclusive evidence.

FMT PRODUCTS & BACTERIAL CONSORTIA

FMT "products" are, however, also in development. These are often referred to as "full spectrum microbiota" products and are considered a type of LBP. Several such products have been successful in late-stage trials for the prevention of recurrence of *C. diff* infection after standard antibiotic treatment for the initial infection.

A similar approach is to use a cocktail or "consortium" of multiple bacterial strains as the drug product. Such consortia products may be composed of hundreds of strains, by reducing from a full-spectrum donor fecal sample, or as little as three strains fermented separately from cell banks before being combined together in a capsule.

FMT products by definition, and many consortia products currently in development, use donor-derived material. This may prove to have important practical limitations, such as variability in the product due to significant inter-individual variability even within healthy donors, reliability of supply, commercial scalability, and risks of infections caused by the transfer of pathogens from donor to recipient requiring rigorous screening and testing.

Some consortium products are manufactured through the fermentation of each constituent strain separately before being combined into a single drug product. Manufacturing complexity thus increases significantly with the complexity of the product. Complex consortia products may also face potential regulatory issues due to agency requirements that the contribution of each component of a drug product be accurately detailed and its inclusion justified.

It may be difficult to tease apart the relative contributions and activity of all strains within a consortium, particularly FMT-like complex donor-derived consortia. The composition of consortia products has typically been based on observations of correlations between the relative abundance of certain bacteria, for example in healthy individuals vs patients with a given disease, rather than known functions of particular strains. As the field has progressed, developers of bacterial consortium products are beginning to consider function more closely, but this still tends to be driven by reverse engineering a mechanism of action based on observations in human studies, rather than direct investigation of specific strains and their impact on host biology.

In developing consortium products, a balance must be struck between, on the one hand, utilizing high-volume dosage forms to ensure a significant number of each strain is administered to the patient (which could adversely affect patient compliance and acceptance of the product, as well as practical considerations of commercial viability), and on the other hand, utilizing more conventional dosage forms (but risking that an ineffective amount of one or more strains will be delivered).

SINGLE STRAIN LIVE BIOTHERAPEUTICS

The history of medicine is typically characterized by refinement from complex beginnings to functional singularity. From

FIGURE 1

4D pharma's Live Biotherapeutics are single strains of gut commensal bacteria that have been originally isolated from healthy human donors and are grown from cell banks at the company's in-house cGMP-certified manufacturing facility, encapsulated for oral administration and selective delivery to the gut where they exert their therapeutic effects.

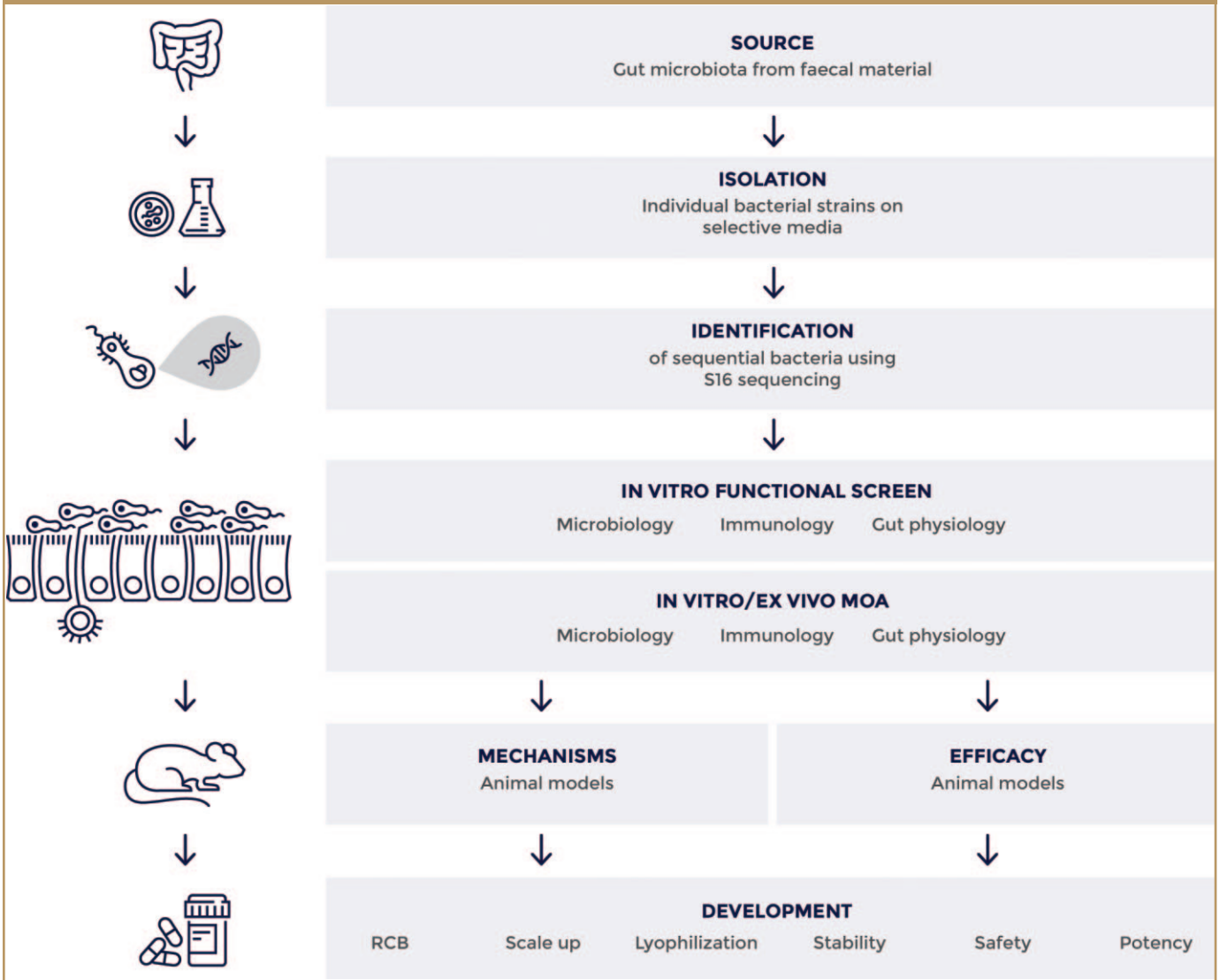
plant extracts to small molecules, from smallpox scabs to mRNA COVID-19 vaccines, from whole plasma to recombinantly produced antibodies, and now from FMT to Live Biotherapeutics – drug development has evolved toward more precise approaches with the goal of fundamentally altering mechanisms of disease.

Functionality in complex organisms exists at different levels – organs, tissues, cells, and molecules. Cells represent the simplest unit of independent biological functionality. Likewise, individual strains of bacteria are the simplest unit of contained functionality within the microbiome. Cells-as-therapies have demonstrated the ability to deliver therapeutically relevant effects "in context." Harnessing and controlling the effects can lead to remarkable results (eg, CAR-T, stem cell therapy, and single strain Live Biotherapeutics).

Selection of a single strain Live Biotherapeutic begins by looking for specific activity against human targets. A panel of candidate strains (originally isolated from healthy human gut microbiome samples) is screened for a particular desired activity or attribute. This may be genetic, metabolic, or through specific functional assays, and such assays may be focused on molecular (activity against a known receptor target), cellular (such as a particular immune cell type or signaling pathway), or phenotypic activity. This process is analogous to small molecule drug discovery.

Focus then turns to understanding how these individual strains act on host biology to exert a therapeutic effect through detailed characterization of mechanism of action and their interaction with human cells through specific pathways. This rational, target- or functionally driven approach has facilitated the expansion of LBPs beyond GI disease, targeting immune-related disease, cancer, and even

FIGURE 2



4D pharma uses its proprietary MicroRx® platform to interrogate its extensive library of bacterial isolates to identify Live Biotherapeutic candidates for a given disease based on a deep understanding of functionality and mechanism.

the central nervous system (CNS).

An additional but often overlooked advantage of single strain LBPs is they can be delivered in a patient-friendly oral dosing regimen. This is in contrast to consortia bacterial products that may involve a high pill burden to deliver a therapeutically relevant dose of each strain. Additionally, because single strain LBPs operate through a well-defined mechanism of action, like a small molecule or biologic, and their activity should be independent of the background microbiota, no pretreatment with antibiotics is required to clear the resident microbiome to make room for colonization.

ENGINEERED BACTERIA

Another quite distinct approach that is typically included within the umbrella of "microbiome therapeutics" because of its use of bacteria as a "delivery chassis" is to engineer bacteria to express heterologous genes for therapeutic activity. A chassis strain is engineered with new, non-native functionality, such as the expression of a therapeutic protein, or heterologous metabolic activity. This approach typically uses well-studied model organisms as the chassis or vector, which have established genetic engineering tools and protocols.

Because these types of engineered bacterial drug products are not naturally occurring organisms, this synthetic biology approach potentially faces a higher safety risk and regulatory hurdle than using wild-type LBPs originally isolated from healthy humans. The FDA's 2016 guidelines include a sub-categorization for "recombinant LBPs," which "raise additional considerations and thus would require additional information to be submitted in an IND."

NON-LIVE BIOTHERAPEUTIC MICROBIOME THERAPIES: BACTERIAL-DERIVED PRODUCTS

Taking the reductionist approach one step further, some companies are looking to bacteria as a source of new drugs, but not as the drugs themselves. This approach centers around identifying and isolating a particular component or molecule produced by a bacterium and developing this molecule itself as the drug product. While this approach does involve bacteria and the microbiome, it is more an expansion of an age-old approach in pharmaceuticals of developing drugs derived from natural sources – think antibiotics first identified from products of other bacteria.

Novel approaches include utilizing biomaterials produced by bacteria, such as extracellular vesicles and small molecule metabolites. One example being pursued is the idea of "molecular mimicry," looking for bacterial proteins that share structural similarities with human proteins or antigens. For example, in cancer indications, bacterial proteins that share similarities with proteins overexpressed by certain cancers have been identified that could trigger an immune response against those antigens, in a therapeutic approach reminiscent of cancer vaccines.

This approach applies a traditional small molecule or biologic development approach to a new source of compounds, the microbiome. Establishing mechanism of action for an isolated molecule may be easier, and more familiar, than for a whole cell or a complex mixture. Similarly, manufacturing of a biologic or small molecule, regardless of its original source of inspiration, fits more comfortably with established traditional CMC infrastructure and processes.

While this approach may reduce some of the uncertainties around a new modality and use of live organisms, it misses out on some of the novel advantages. Recombinantly or synthetically manufacturing a single molecule and delivering it in isolation negates any benefits from "delivery in context" offered by Live Biotherapeutics. This may include physical localization, such as a bacterium's ability to penetrate the mucus layer and access human epithelial and immune cells, as well as the context of other co-signaling molecules also being produced by a living, metabolically active bacterium, which may be critical to potentiating or augmenting the activity of the molecule in question.

MICROBIOME-TARGETED DRUGS

Lastly, other companies are approaching the microbiome as a novel target, rather than a source of novel drugs themselves. This typically falls into two categories – subtractive and additive. Subtractive microbiome-targeting therapies are broadly aligned with the historic perception of bacteria as disease-causing pathogens, with the goal of removing or inhibiting specific bacteria, groups of bacteria, their products or activity believed to have a role in the cause or progression of disease. This is typically achieved through small molecules or bacteriophage to specifically kill or inhibit disease-associated bacteria, or molecules designed to sequester, metabolize, or otherwise remove bacterial products also associated with disease.

Additive microbiome-targeting therapeutics are drug products that do not comprise Live Biotherapeutics but are intended to act on the resident microbiome to modulate either its composition or metabolic output. Typically, such products are prebi-

otics – oligosaccharides that are preferentially used as energy sources by certain bacteria to increase their relative abundance within the microbiome. Similarly, prebiotics may be used to modulate the metabolic output of the microbiome more so than its relative composition. A potential issue for compliance and ultimately the commercial success of medical prebiotics is the large doses required to achieve meaningful modulation of the microbiome. Such prebiotics currently in mid-stage clinical phase are administered in doses measuring tens of grams rather than milligrams.

4D PHARMA'S DRUG DISCOVERY MICRORX® PLATFORM

Rather than try to define a "healthy" microbiome, 4D pharma set out to apply the scientific principles and rigor of drug development to this exciting new field, investigating the mechanisms of specific strains of bacteria and their interactions with host biology, and exploiting this in-built therapeutic activity. Based on over 2 decades of world-leading research into the role of the microbiome and its influence on our immune system, 4D pharma has built a proprietary platform – known as MicroRx® – to rapidly select those bacteria that have a therapeutic effect in specific diseases. This sector-leading platform has allowed 4D pharma to uncover the potential of using single strains of bacteria to address a wide array of medical challenges that are not just gut-related but systemic, from GI to cancer to neurodegenerative disorders.

MicroRx is able to rapidly interrogate 4D pharma's proprietary library of bacterial isolates for specific therapeutic functionality. We understand the microbiome is a complex system often perceived as a "black box," and therefore the need to demonstrate what the bacteria are doing and how they impact disease biology are critically important for effective drug development. This reflects the natural progression throughout the emergence of any new modality – refining complex mixtures to simpler and more precise therapeutic units. Applying this concept to the microbiome has always been 4D pharma's focus, and is now increasingly reflected across the microbiome therapeutics space as drug developers move away from "full-spectrum" microbiota products typically based on observational correlations toward more precise, targeted microbiome-derived therapeutics based on mechanisms of action.

PROGRESSION OF LIVE BIOTHERAPEUTICS & CONSIDERATIONS FOR THE FUTURE

In comparison with other therapeutic classes, such as antibodies or gene therapy, the progress that has been made with Live Biotherapeutics to date has been rapid. For the field to maintain this rate of progress and to establish LBPs as a mainstay in the treatment of patients across a variety of diseases, a number of key questions need to be addressed. Compelling clinical data is beginning to emerge in gastrointestinal disease and oncology, but to realize the full potential of microbiome therapeutics, this needs to be continued in multiple settings and larger clinical studies. And as LBPs progress through clinical development toward approval, manufacturing is increasingly recognized as a critical factor to the realization of this new class of drug.

Based on the significant progress that has been made by 4D pharma and others in only the past 10 years, it is realistic to expect that LBPs could soon become an important part of clinicians' armory for the treatment of many different diseases. The field is tantalizingly close to achieving those all-important first product approvals. It is exciting to be part of the establishment of a new class of safe and effective medicines expected to bring lasting benefit to millions of patients in need and to gain widespread acceptance in the clinical community. ◆

BIOGRAPHY

Duncan Peyton has a proven track record in identifying, investing in, and growing businesses within the pharmaceutical sector. He was the founder of Aquarius Equity, a specialist investor in businesses within the life sciences sector, which provided investors with access to innovative, high growth potential companies that delivered significant capital growth. He started his career in a bio-science start-up business, which ultimately went on to list on the London Stock Exchange, subsequently qualified as a corporate finance lawyer with Addleshaw Goddard, then Addleshaw Booth & Co, and later joined 3i plc as an investment manager. He founded Aquarius in 2005, which made founding investments into Nanoco Technologies Limited, Auralis Limited (subsequently sold to ViroPharma), Tissue Regenix Group plc, Brabant Pharma (subsequently sold to Zogenix, Inc) and C4X Discovery plc. He is a Co-founder of 4D pharma plc and has served as Chief Executive Officer since 2014.

Specialty CDMO

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

CDMO Services

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

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Artcraft Health is a leading patient engagement and education agency that takes a holistic approach to demonstration device development and training. Our goal is to elevate and support the entire patient experience through educational onboarding initiatives involving both clinicians and patients. This is how we ensure certainty of use and long-term success. We help patients, caregivers, clinicians, and healthcare providers – who are either counseling patients or adopting new therapies and drug delivery methods – build the skills, knowledge, and motivation they need for a successful outcome. We excel at simplifying complex delivery methods and packaging them into easy-to-understand educational materials that help patients comply with dosing and administration. So we not only provide the highest quality device, but also aid in the launch strategy for commercial teams. For more information, visit Artcraft Health at **www.artcrafthealth.com/demo-devices.**

Formulation Development

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

OptiDose® Design Solution

Catalent's OptiDose Design Solution integrates pharmaceutics, critical CMC and DMPK parameters, and dose form design target patient characteristics to create differentiated treatments that are successful for innovators, patients, and healthcare professionals. The methodology combines data-driven scientific tools with Catalent's extensive development expertise. Patient needs and market realities are considered upfront in the process, to guide development decisions and ensure a product with the optimal combination of patient acceptance and adherence, as well as differentiation from existing standards of care. By taking an agnostic evaluation of a molecule against potential dose form technologies, products can be designed to maximise their potential using Catalent's broad technology toolkit, which includes advanced softgel solutions, as well as Zydis® orally dissolving tablets, and FlexDose™ stick pack solutions. For more information, contact Catalent Pharma Solutions at (888) SOLUTION or visit **www.catalent.com.**

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Celanese

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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.**

Differentiated Injectable Delivery

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

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

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Getting your delivery device approved by regulators is important, right? Then come to **Medical Engineering Technologie**s for your validation and stability testing. We only test medical devices, and we know about medical devices. We will understand your needs and efficiently deliver testing and advice from the start of your project right through to your submission. Services include: biocompatibility and chemical characterization, dose delivery accuracy, e and I studies, formulation stability, mechanical performance, RLD comparisons, sterile barrier verification, human factors studies, and lots of good advice. We will make sure that your project moves rapidly forward. For more information, visit Medical Engineering Technologies at **www.met.uk.com.**

Functional Chemicals

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

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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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PharmaCircle is a 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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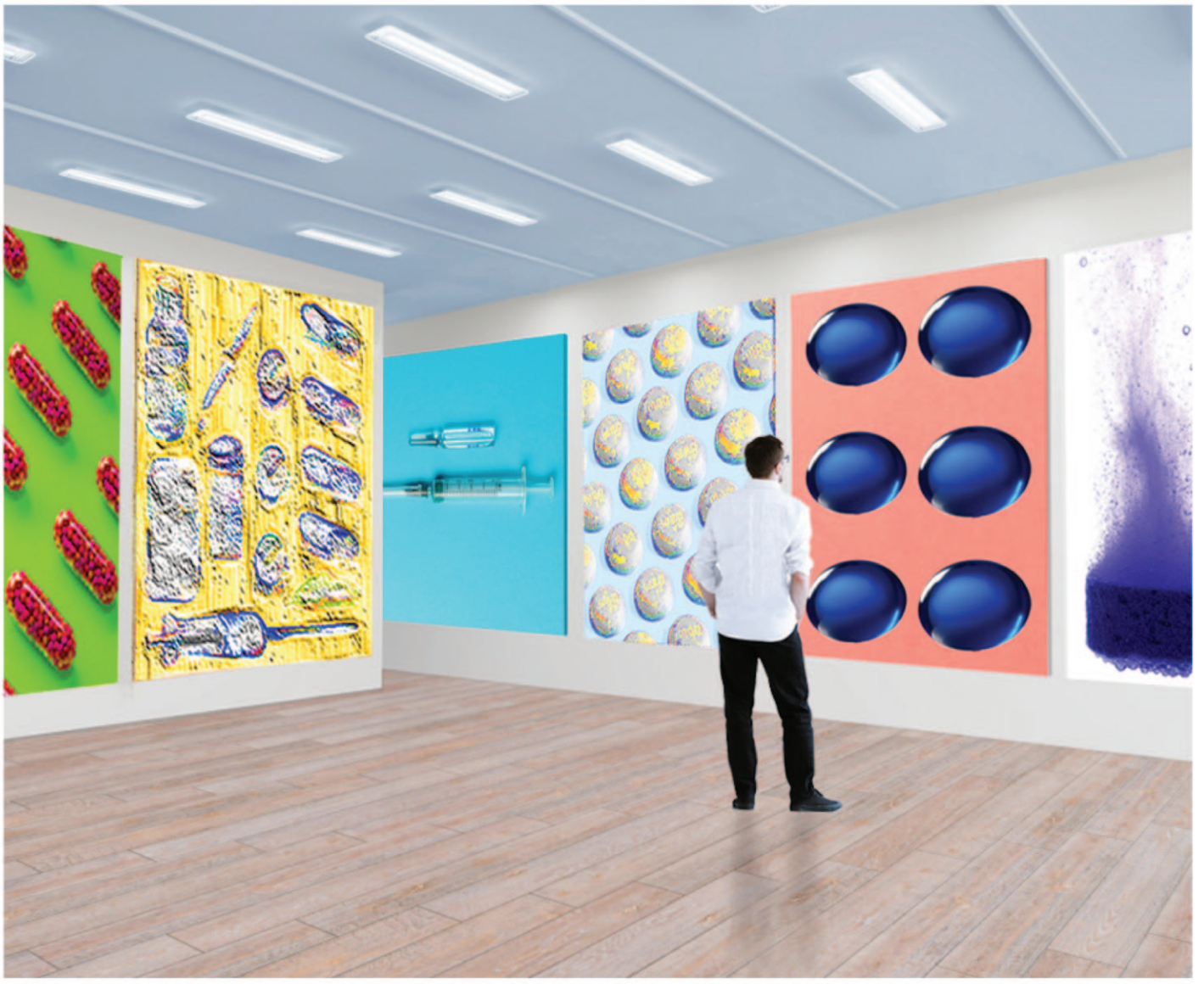
Artcraft Health	50		artcrafthealth.com/demo-devices
Ascendia Pharma	9	(732) 640-0058	www.ascendiapharma.com
Catalent Pharma Solutions	76	(888) 765-8846	www.catalent.com
Celanese	11	healthcare@celanese.com	www.healthcare.celanese.com
Credence MedSystems, Inc.	15	(844) 263-3797	www.CredenceMed.com
DDL	13	(952) 941-9226	https://www.ddltesting.com
Drug Development & Delivery	4	(973) 263-5476	www.drug-dev.com
Emergent CDMO	12	(800) 44- 4225	https://emergentCDMO.com
Enteris Bio	10	(973) 453-3520	www.enterisbiopharma.com
Gattefosse	2	(201) 265-4800	www.gattefosse.com
Medical Engineering Technology	25	sales@met.uk.com	www.met.uk.com
Mitsubishi	3		https://www.mgc.co.jp/eng/products/abd/oxycapt.html
Nemera	27	information@nemera.net	www.nemera.net
Owen Mumford	5	pharmaservices@owenmumford.com	https://www.ompharmaservices.com/
PDA	41		pda.org/2022ups
PharmaCircle	42,43	(800) 439-5130	www.pharmacircle.com
SHL Medical	33	digital@shl-medical.com	shl-medical.com



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