Drug Development & Delivery

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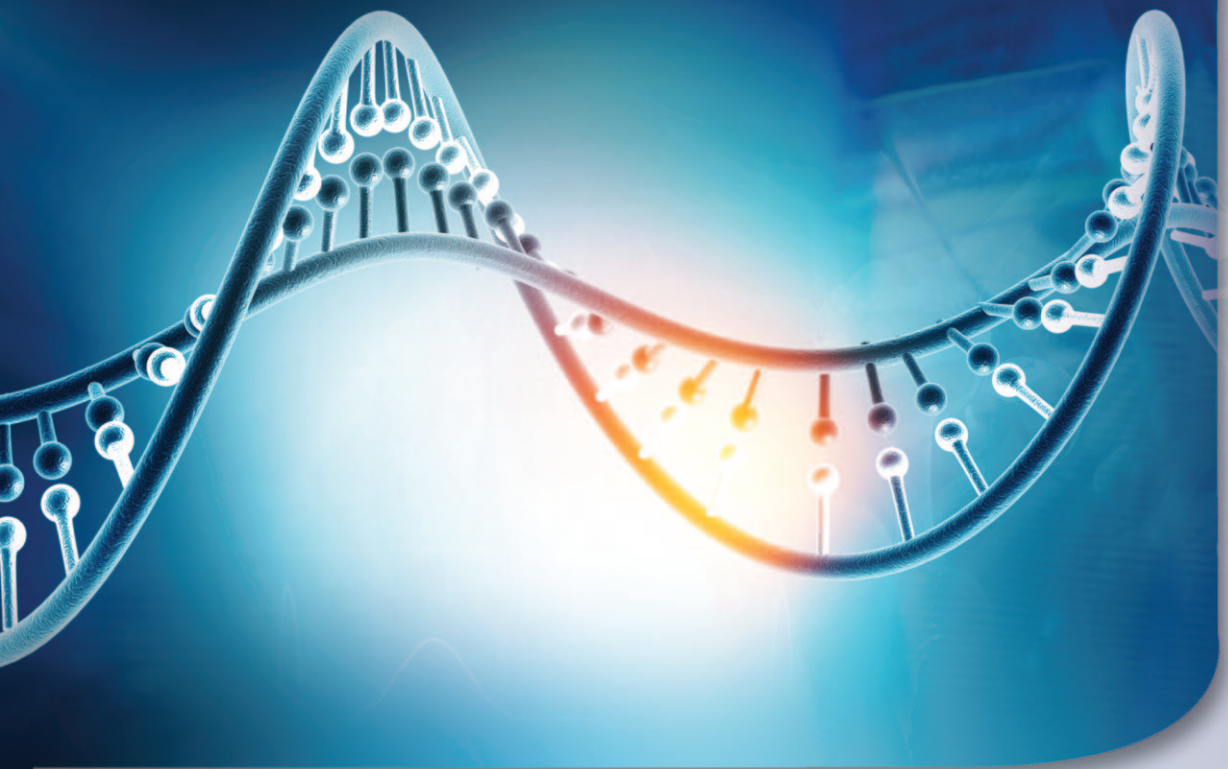
The Promise of siRNA Therapies



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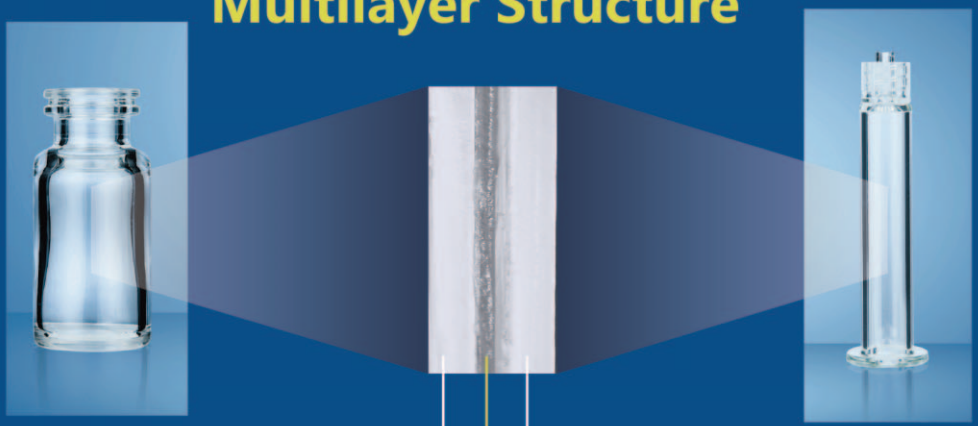

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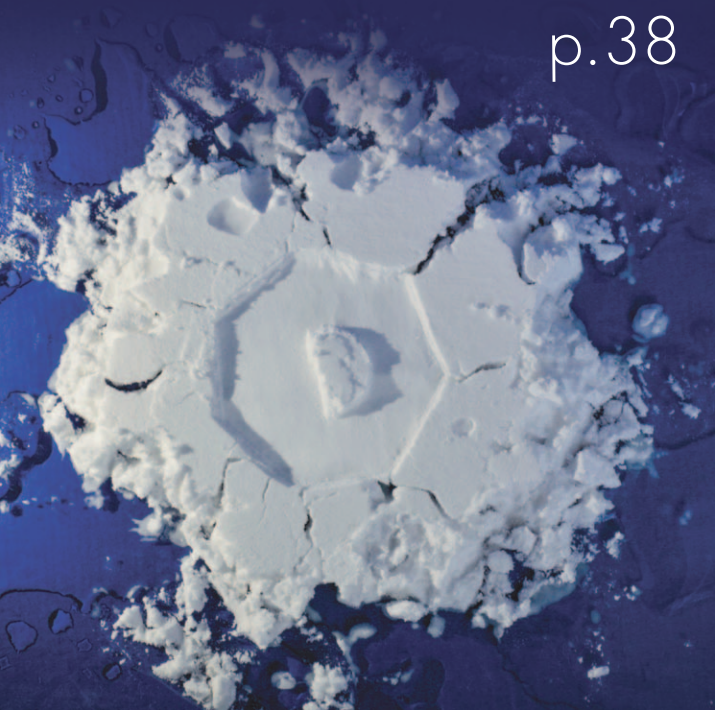

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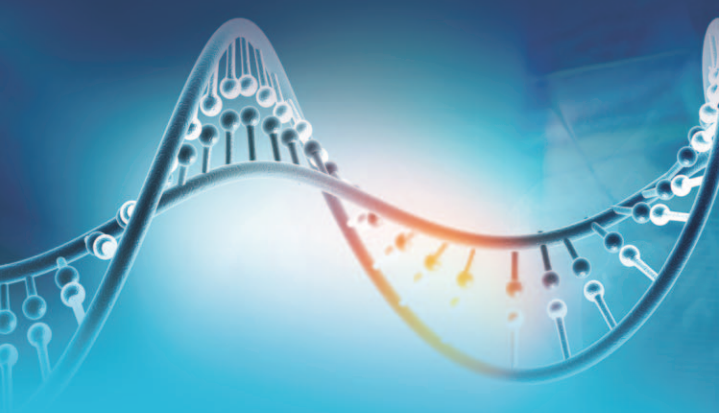
The Promise of siRNA Therapies

"The selection of diseases and gene targets for siRNA therapies can appear daunting because of the myriad possibilties: of the approximately 30,000 genes in the human genome, the liver expresses about 14,000, and only 1% of those are targeted by publicly disclosed siRNAs. This leaves a vast "white space" of potential targets and therapeutic opportunities. When stepping into this space, Silence applies two key criteria to select diseases and targets for our mRNAi GOLD™ platform."



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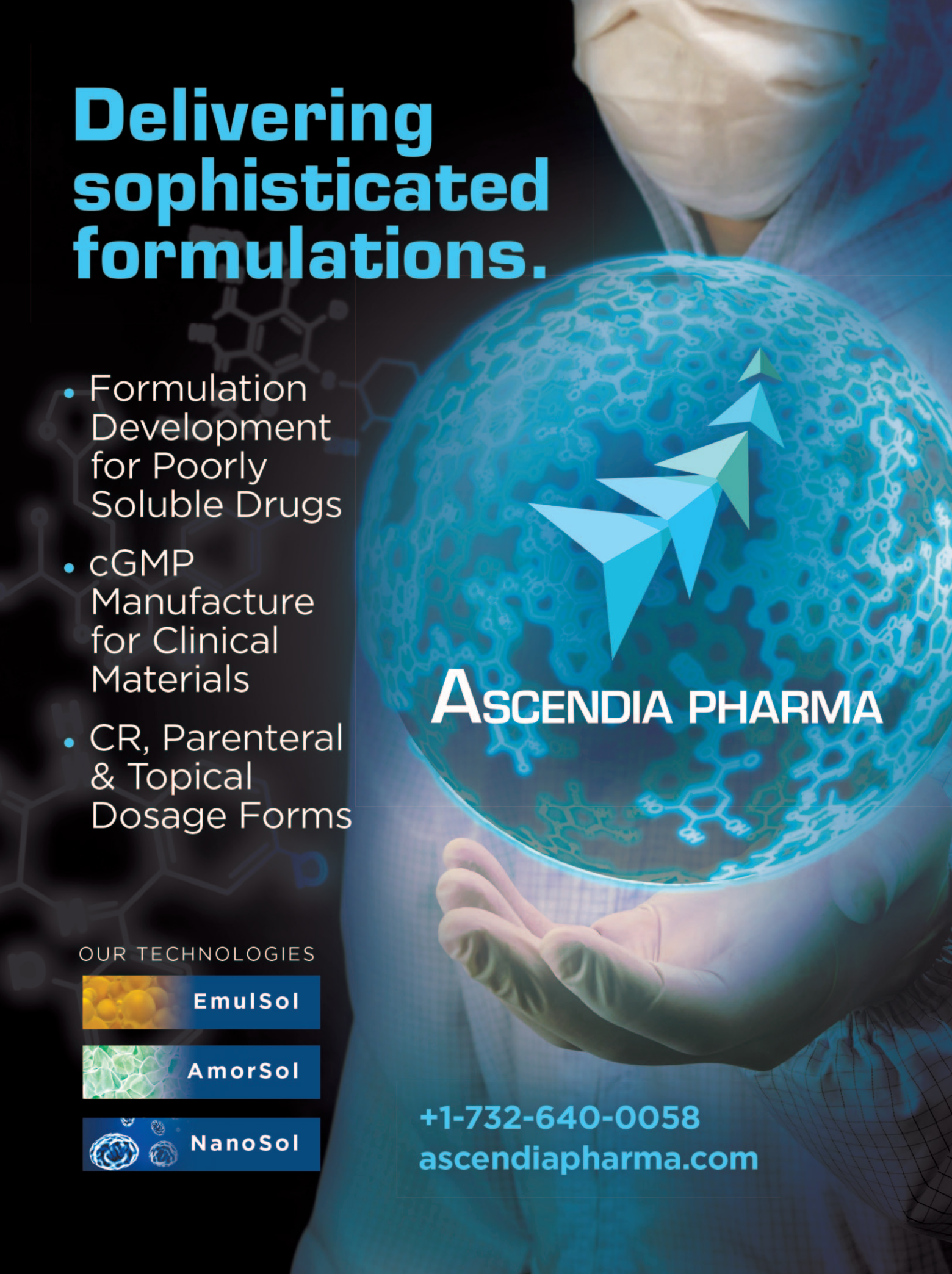
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Pharmazz Inc. Announces Positive Results of Phase 3 Clinical Trial Evaluating Sovateltide as a Treatment for Acute Cerebral Ischemic Stroke

Pharmazz, Inc. recently announced positive topline results of its Phase 3 clinical trial evaluating sovateltide as a treatment for acute ischemic stroke. The data at 90 days showed mRS had a significantly greater number of patients with an improvement of ≥2 points on mRS ($p=0.0045$), mRS with a significant median score reduction ($p=0.0078$) and a significantly greater number of patients with an improvement of ≥6 points on NIHSS ($p=0.0330$). In addition, sovateltide was well tolerated, with no drug-related adverse event reported. The results have prompted Pharmazz to apply for marketing authorization from the Indian Central Drugs Standard Control Organization (CDSCO). In addition, the full data set is expected to be presented at a future medical conference. Sovateltide is a highly selective endothelin B receptor agonist that increases blood flow, shows anti-apoptotic activity, protects neural mitochondria, and produces neurovascular remodeling.

The randomized, double-blind, parallel, placebo-controlled Phase 3 clinical trial conducted in India enrolled 158 adult acute ischemic stroke patients who were provided the standard of care and treated with either vehicle or sovateltide. Ischemic stroke was radiologically confirmed either by computed tomography (CT) scan or magnetic resonance imaging (MRI) prior to enrollment. Alberta Stroke Program Early Computed Tomographic Score (ASPECTS) mean value was similar in the control (7.44) and sovateltide (7.61) groups indicating that the extent of infarction was similar in both the groups. Patients could be enrolled if presenting up to 24 hours after onset of symptoms and with a modified Rankin Score (mRS) of 3 to 4 and an NIHSS (NIHSS Level of Consciousness (1A) <2) score of greater than 5. The primary objective was to determine the neurological outcome based on mRS score, NIHSS score, and BI scale score from day 1 through day 90. In addition, secondary endpoints at 90 days post-treatment include a change in the quality of life (EuroQol-EQ-5D), stroke-specific quality of life (SSQOL), the incidence of ischemic stroke recurrence, and incidence of mortality. More information, including additional primary and secondary outcome measures, can be found at NCT04047563.

The change in mRS post-randomization at 90 days is the most important and is expected to be the primary endpoint for US Phase 2/3 clinical trials. Results show that the distribution of the mRS score at 90 days in the intention-to-treat population an ordinal shift across the range that highly favors sovateltide therapy. In addition, the number of patients with mRS of 0 to 2 was 23.4% higher in the sovateltide compared to the control group ($p=0.0036$). Treatment with sovateltide was well tolerated, and results on the other endpoints will be presented at an upcoming medical conference.

Sovateltide is being evaluated in other acute ischemic indications. In addition, the company recently applied for an Investigational New Drug application from CDSCO for a multicenter, randomized, placebo-controlled Phase 2 clinical trial in hypoxic-ischemic encephalopathy in neonates.

Clearmind Medicine & SciSparc Collaboration Yields Positive Results for its Psychedelic Combination Treatment

Clearmind Medicine Inc. recently announced positive safety profile results from its joint preclinical trial with SciSparc Ltd. The trial evaluated the proprietary combination of Clearmind's proprietary psychedelic molecule MEAI and SciSparc's CannAmide for treating alcohol consumption.

"We are extremely pleased with these positive results that once again strengthen our belief in the potential of our novel propriety psychedelic molecule MEAI," said Dr. Adi Zuloff- Shani, Clearmind's Chief Executive Officer. "The results continue to suggest a high safety profile of the joint venture psychedelic combination treatment. We plan to further explore the safety and efficacy of combining our novel technology with Clearmind's novel molecule."

Earlier trials successfully showed a significant dose-dependent effect for MEAI treatment in reducing alcohol consumption in mice, with an additional significant effect achieved when combining CannAmide with a lower sub-effective MEAI dose. These positive results follow previously announced results showing that alcohol consumption was significantly reduced following treatment with MEAI at a dose of 40 mg/kg and higher ($p<0.01$) compared to consumption before treatment.

A histopathology assessment was conducted to determine safety of the proprietary combination of MEAI and CannAmide vs. control (mice that were not exposed to alcohol). Several organs (heart, lungs, liver, kidneys, brain, pancreas, spleen, and thyroid gland) were harvested from all experiment groups ($n=3$-5 per group) and evaluated for impairment. The severity of impairments was scored by a 5-point scale by a qualified blinded toxicologist (Schafer et al., Toxicol Pathol 2018, 46:256-265). Results indicated a high safety profile of the combination treatment with no treatment-related changes observed.

Alcohol consumption was significantly reduced following dual treatment with 25 mg/kg CannAmide in addition to MEAI at a dose of 20 mg/kg and compared to consumption before treatment. The mice were provided with 20% alcohol solution for 24 hours, three times a week for 7 weeks, and were treated every day with MEAI or MEAI/CannAmide during the last 2 weeks of alcohol treatment. The alcohol consumption was measured by weighing the alcohol bottles before and after; water consumption was measured similarly in parallel.

Clearmind is a biotech company focused on the discovery and development of novel psychedelic-derived therapeutics to solve widespread and underserved health problems, including alcohol use disorder, binge eating and depression. The Israeli-Canadian company holds several patents for the non-hallucinogenic compound MEAI. The company intends to seek additional patents for its compounds whenever warranted and will remain opportunistic regarding the acquisition of additional intellectual property to build its portfolio. The company's intellectual portfolio currently consists of five patent families. The company intends to seek additional patents for its compounds whenever warranted and will remain opportunistic regarding the acquisition of additional intellectual property to build its portfolio.

SciSparc Ltd. is a specialty clinical-stage pharmaceutical company led by an experienced team of senior executives and scientists. Our focus is on creating and enhancing a portfolio of technologies and assets based on cannabinoid pharmaceuticals.

N4 Pharma Highlights Potential of Nuvec as Gene Therapy Delivery Platform

A recent preclinical *in-vivo* study found that Nuvec – N4 Pharma's novel silica-based nanoparticle – formulated with TNF-α pDNA oncotherapy, suppressed tumor growth and improved survival of treated mice compared to untreated controls.

This research has added to growing evidence of Nuvec's suitability for clinical use in oncology, gene therapy, and protein replacement due to its ability to load and protect multiple plasmids (both large and small); its ability to deliver a payload to the appropriate cells and to effect transfection and release; and its thermostability (Nuvec can be dried, stored at room temperature, and reconstituted without degradation of DNA).

TNF-α (Tumour Necrosis Factor) cytokine has cytotoxic effects on cancer cells but cannot be easily used clinically due to its high toxicity. Nanoparticle-mediated preferential delivery to the tumor (possibly due to the enhanced permeability and retention [EPR] effect) of non-toxic TNF-α precursor in the form of DNA, could present a viable oncotherapeutic strategy, making TNF-α an appropriate compound as proof of concept for demonstrating Nuvec's suitability in this space. It is anticipated that other compounds would be trialled with Nuvec in future studies prior to clinical trials.

Nuvec has a novel irregular surface structure that simply and effectively binds and protects the RNA/DNA to help delivery to the cell membrane. Once inside the cell, via an endocytotic process, the RNA/DNA is released to enter the cellular machinery, resulting in protein transcription and delivery of an immune response. Nuvec can be optimized to produce a consistently monodispersed product once loaded.

Dr. David Templeton, Technical Director, N4 Pharma, said "The researchers at the CRO formulated colloidally stable Nuvec-TNF-α pDNA polyplexes, which successfully mediated gene transfer to the cells and translation to the functional cytokine *in vitro*, and generated an anti-tumor response in an *in vivo* mouse tumor model. This provides clear evidence that Nuvec has the potential to deliver plasmids with anti-tumor effects in vivo. Our next phase of work involves exploring the dose response curve with the TNF alpha plasmid and evaluation of other potential nucleotide-based therapies. We are actively looking for/seeking compounds with commercial application to trial with Nuvec."

Nigel Theobald, CEO, N4 Pharma, added "To date, companies developing oncology drugs or vaccines have had a limited choice of delivery systems to work with. Lipid nanoparticles, viral vectors, or electroporation, being the established choices. Although these can produce good results, they can also cause undesirable side effects, such as accumulation in the liver, the infection of healthy cells, and the stimulus of unwanted systemic immune activity. In addition, it is important to remember that electroporation remains very expensive and complicated to administer. We are pleased with these latest findings that add further weight to the potential of Nuvec as a viable alternative delivery system for use in cancer treatments and vaccines."

Lonza & Israel Biotech Fund Collaboration Framework Agreement to Support Biologics & Small Molecules Development & Manufacture for Portfolio Companies; IBF to Facilitate Access to Israeli Market

Israel Biotech Fund, a venture fund investing in Israeli and Israeli-related biotech companies, and Lonza, a global development and manufacturing partner to the pharma, biotech and nutrition industries, recently announced a framework agreement. Lonza will add value to IBF through pre-investment due diligence support and offer IBF's portfolio companies with tailored advice, flexibility, and services for the development and manufacturing of biologics and small molecules. IBF will provide Lonza with access to IBF's portfolio companies and broad network in the biotech industry in Israel.

The agreement aims to broaden the scope of services provided by Lonza to pharmaceutical companies in the Israeli ecosystem and an opportunity to support the unique needs of these companies looking to simplify and de-risk the development of their molecules. This is particularly relevant to the Israeli biotech industry, where the number of biotech start-ups established every year has averaged 150 in the last decade.

In Israel, a country that is slightly smaller than the state of New Jersey, there were more than 1,750 life science companies active at the end of 2020, many of which are start-ups and small biotech companies. IBF is an investment fund dedicated to investments in and development of the biotech industry in Israel. Since its inception in 2015, IBF has played a key role in the Israeli Biotech ecosystem. It has vast exposure to and familiarity with the market and key players in the Israeli pharma industry, as well as most biotech companies and projects.

Lonza will advise IBF in its due diligence review of candidate biotech targets and provide a tailored offering, advice and services to IBF's portfolio companies targeting innovations in the healthcare sector focused on developing therapeutic assets and disruptive platforms.

Pnina Weitz, Global Head of Venture Capital Business Development and Relationship Management, Lonza, commented "We chose to collaborate with IBF, a leading investment fund in Israel, due to their unique investment strategy, broad network and approach. We are excited to implement this framework agreement that will provide IBF and their portfolio companies with services and expertise across multiple modalities. IBF's network will allow Lonza to benefit from these connections and offer services and expertise across multiple modalities. Lonza's customized and scalable solutions in the development and manufacture of both biologics and small molecules will allow these companies to leverage our global network and experience and focus on what they do best – developing innovative and transformative treatments."

The offering comprises Lonza's expertise and technology that accelerates timelines while mitigating risks of developing and manufacturing molecules ranging from monoclonal antibodies, complex proteins, and small molecules to antibody-drug conjugates. The integrated approach to drug substance and drug product development and manufacturing across various platforms significantly simplifies the supply chain, reduces process complexity, and allows for shortened development timelines.

Croda Announces the New Pharma Business

Croda recently announced that its Health Care division will now become Croda Pharma, bringing its core speciality excipient portfolio together with the recent acquisition, Avanti Polar Lipids and its Adjuvant Systems arm, all under one business.

Croda Pharma has seen exceptional growth across its high purity excipients and vaccine adjuvants area and more recently announced the acquisition of Avanti Polar Lipids, bringing in a strong pipeline of novel lipids and formulation capabilities in-house.

The company continues to expand its breadth in solutions, enabling over 250 on-going clinical projects, targeting a range of therapeutic areas including oncology, malaria, HIV, and diabetes.

Last week, the company was awarded the prestigious Best Supplier for COVID-19 Vaccine Development at BVOIA Vaccine awards, 2022. The awards give recognition to exceptional biologics and vaccine experts, and technologies that facilitate R&D and biologics manufacturing excellence.

This comes just days after the company announcement of the new strategy and its promise "Empowering biologics delivery" and after Croda Pharma and Avanti Polar Lipids presented at the World Vaccines Congress, Washington DC, on their collaboration and work supporting vaccines globally.

Freek Snieders, Senior Vice President – Croda Pharma, said "This is exactly what Croda is all about – smart science to improve lives. Our great achievements and focus on innovation and deep formulation expertise has continued to propel us forwards as a leading partner for Biopharma. Becoming 'Croda Pharma' is a natural progression and represents the joining of three powerful business areas. It represents a single partner that will empower biologics drug delivery for years to come. That is Croda Pharma."

Croda Pharma continues to expand its offering in innovative speciality excipients, vaccine adjuvant systems, and lipids, in order to support the Biopharma industry with unparalleled quality and expertise.

Established in 1925, Croda is the name behind sustainable, high-performance ingredients and technologies in some of the world's most successful brands: creating, making and selling speciality chemicals that are relied on by industries and consumers everywhere.

Croda is a FTSE 100 company with over 5,500 passionate and innovative employees, working across manufacturing sites and offices around the world with a shared Purpose to use Smart science to improve lives™. As part of this Purpose, and with around two thirds of its organic raw materials already from bio-based sources, Croda has committed to be the most sustainable supplier of innovative ingredients, becoming Climate, Land and People Positive by 2030.

Croda Pharma is a leading partner for the development of excipients and the supply of high purity materials for pharmaceutical formulations. The company is focused on empowering biologics drug delivery, through its adjuvant systems, small molecule, protein, and nucleic acid delivery platforms. With a wide range of solutions for both human and animal health markets, the pharmaceutical portfolio is unsurpassed in its excellence. Croda Pharma's products, along with its in-house formulation and regulatory expertise, allows the company to meet its customers' most demanding formulation needs.

MannKind Corporation Announces Agreement to Acquire V-Go Insulin Delivery Device From Zealand Pharma

MannKind Corporation recently announced it has entered into an agreement with Zealand Pharma A/S to acquire V-Go for $10 million, with additional sales-based milestones plus the cost of certain inventory. The acquisition of V-Go allows MannKind to expand its portfolio and strengthen its commitment to providing innovative mealtime diabetes solutions.

"MannKind is passionate about being a leader in mealtime control to address this unmet need within the diabetes community," said Michael Castagna, PharmD, Chief Executive Officer of MannKind Corporation. "This acquisition strategically leverages our infrastructure in the diabetes space and positions MannKind's endocrine business for additional growth."

"This transaction is an important step forward in executing on the strategic changes we announced at the end of March, to find partners for our commercial products and refocus our priorities on R&D," said Adam Steensberg, MD, Chief Executive Officer of Zealand Pharma. "We believe we have found the right partner to fully leverage the value of V-Go and ensure continued availability of the product by patients and prescribers."

V-Go is a once-daily, wearable, insulin delivery device that helps provide blood sugar control for everyday lifestyles. Designed to be patient-friendly, V-Go is worn like a patch and eliminates the need for taking multiple daily shots.

"The easy click-and-go mechanism of V-Go and its ability to be flexibly placed on your body each day aligns with our mission of providing products that allow patients living with diabetes to experience life without limits," said Alejandro Galindo, Executive Vice President, Endocrine Business Unit for MannKind Corporation. "V-Go joins our ultra rapid-acting inhaled insulin product, Afrezza, in expanding MannKind's portfolio of products that change the way diabetes is treated."

The acquisition of V-Go by MannKind is anticipated to close in May 2022, subject to the satisfaction of certain closing conditions.

MannKind Corporation focuses on the development and commercialization of inhaled therapeutic products for patients with endocrine and orphan lung diseases. MannKind is currently commercializing Afrezza (insulin human) Inhalation Powder, the company's first FDA-approved product and the only inhaled ultra rapid-acting mealtime insulin in the United States, where it is available by prescription from pharmacies nationwide. Afrezza is also available by prescription in Brazil, where it is commercialized by the company's partner, Biomm SA. MannKind was established in 1991, and is located in Danbury, CT, and Westlake Village, CA. The company also employs field sales and medical representatives across the US. For more information, visit mannkindcorp.com.

Gerresheimer Boosts Global Production Capabilities With New State-of-the-Art Facilities in India

Gerresheimer has significantly ramped up its glass and plastic production capacities in India. A new modern plant to produce high quality plastic containers and closures was built at the Kosamba site, and glass production received a new state-of-the-art and sustainable furnace technology. Both innovations were ceremonially commissioned by the management on the same day in April.

By adding capacities in India, Gerresheimer intends to ensure consistent supply for critical pharma and healthcare facilities supporting increased packaging demand and public health. Gerresheimer already operates production facilities, including Triveni and Neutral Glass, which the company acquired in 2012. The four highly specialized Indian plants belong to the Gerresheimer Group's worldwide production network. The plants are equipped with high technology manufacturing process for production of pharmaceutical primary packaging made of plastic, moulded and tubular glass.

"These new investments enable us to serve our customers now locally with combined product solutions across all Gerresheimer divisions. We have special expectations for revenue growth in India, with more capacity we are closer to reaching our goals", said Niels Düring, Global Executive Vice President, Plastic Packaging.

Gerresheimer has installed the latest Type I Borosilicate melting furnace for flint and amber glass production using cross-fired oxygen technology and an increased portion of electric heating to melt our new Barium free type I glass formulation. This new state of the art furnace is equipped with newest production machines also having most sensitive inspection equipment following the Gerresheimer moulded glass production standards. "With this technology, we will substantially enhance our product quality and address additional market segments", said Stefan Rieder, Global Senior Vice President Commercial Moulded Glass.

Gerresheimer ensures full conformity of its products and follows the European pharmacopoeia, the United States pharmacopeia and meets YBB requirements for China and FDA registration with a Drug Master File as the standard. The production operations are carried out in sanitized rooms. Gerresheimer applies the rules of Good Manufacturing Practice (GMP) and is classified in accordance with ISO standards.

Gerresheimer is a leading global partner to the pharma and healthcare industry. With specialty products made of glass and plastic, the company contributes to health and well-being. Gerresheimer is represented worldwide and produces with around 10,000 employees wherever its customers and markets are. With plants in Europe, North and South America and Asia, Gerresheimer generates sales of around €1.4 billion. Its wide range of products includes pharmaceutical packaging and products for the simple and safe administration of medicines: Insulin pens, inhalers, micropumps, prefillable syringes, injection vials, ampoules, bottles and containers for liquid and solid medications with closure and safety systems as well as packaging for the cosmetics industry.

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2021 Global Drug Delivery & Formulation REPORT

Part Three of a Three-Part Series

Part 1: A Review of 2021 Product Approvals

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

Part 3: Drug Delivery and Formulation Pipeline Trends

By: Kurt Sedo, Vice President Operations, and Selda Candan, Vice President Data Analytics, PharmaCircle LLC

Introduction

What immediately pops out when surveying the pharmaceutical product development pipeline is a slowdown in pipeline growth at all stages of clinical and non-clinical development. For products not yet in the clinic, Research and Preclinical, there was a 7% growth rate last year versus an average of 16% to 22% throughout the past 6 years. Clinical-stage annual pipeline growth that averaged 6% to 14% the past 6 years slowed to 3% to 6% this past year. The most obvious reason for the drop in pipeline growth is COVID-19. With companies restricted in terms of operations, and medical institutions focused on treating COVID-19 patients while limiting hospital access, there was little capacity for the initiation of new clinical trials. Even existing trials were slowed down by recruitment issues. This implied that fewer products would be entering the clinic and fewer products transitioning from one stage of development to another.

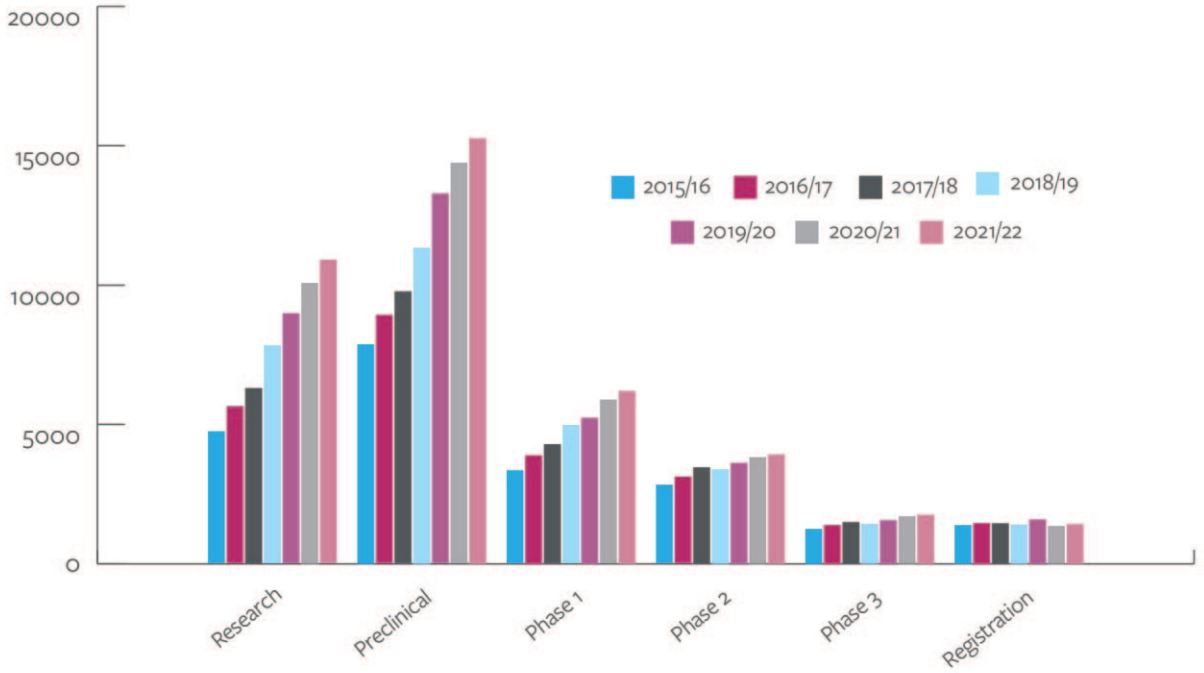
It may also be that companies are showing more discipline with respect to the products they are selecting to enter clinical trials and those they are choosing to advance in the clinic. Several notable product failures in the past year may have also caused companies to pause and rethink their development plans. While a large number of emerging companies received considerable financing, venture and public market, many were not in a position to actually use the funding to advance their programs. It is likely that 2021 will be turn out to be aberration in terms of pipeline growth. Strong funding and the considerable number of medical needs will continue to drive innovation.

Beyond the slowdown in the growth of the pharmaceutical product pipeline, there were few surprises regarding the nature of the pipeline itself. Small molecule therapeutics continued to be the leading molecule type in development this past year, accounting for 59% of all molecule types, although its share continues to shrink. Injection continued to be the favored delivery route in 2021 with a 52% share of all clinical-stage products. Even though small molecules can generally be delivered orally, the large number of cancer and infectious disease products lean on injection routes to optimize efficacy and safety by permitting greater control over administration and distribution.

Whether 2021 was an aberration or the new normal is a question that will be answered over the next few years. The following pages provide additional insights into the nature of the current pipeline in terms of development phase, delivery route, molecule type, and disease area taken from PharmaCircle's Pipeline Dynamics module.

Pipeline growth, from Research through Phase 3, was sharply attenuated in 2021

Pharma Pipeline Product Development, 2015/16 to 2021/22 (Most Advanced Phase)



Source: PharmaCircle Pipeline & Products Intelligence Module (Pipeline Dynamics). The 2021/22 data reflects the pipeline figures for March 31 of the later year, for example, the 2021/22 dataset reflects the pipeline March 31, 2022.

The growth of early stage pharmaceutical products, Research and Preclinical, continues to outpace the growth of clinical-stage products. This is largely accounted for by investor interest in supporting new companies at the ground floor, often with prospects but not yet clinical stage programs. Growth in the past year for Research- and Preclinical-stage products was 8.0% and 6.3%, respectively. This compares with average annual growth rates of 22% and 16% throughout the previous 6 years.

The increase in the Phase 1 (5.8%), Phase 2 (2.5%), and Phase 3 (3.1%) pipelines for the year ending March 31, 2022, fell well short of the 14.3%, 6.6%, and 6.7% average annual growth rates for the previous 6 years.

The reasons for the slowdown in the pipeline growth are many with the most obvious being the negative global impact of COVID-19 on clinical trial initiation. After a flurry of exciting product development announcements throughout the past few years, there was a more sober mood in the past year with a number of high-profile products, often with inflated prospects, failing to deliver expected clinical results.

Small molecule therapeutics remain in the majority but with a shrinking share

Molecule Type as a Share of All Clinical Stage Products, 2021/22

	Phase 1	Phase 2	Phase 3	Share of All Clinical Products (2021/22)	Share of All Clinical Products (2015/16)
Small Molecule	49%	60%	63%	59%	66%
Antibody	14%	11%	14%	12%	9%
Protein	6%	8%	9%	6%	8%
Peptide	5%	6%	5%	5%	6%
Cell & Gene Therapy	16%	6%	4%	10%	8%
Oligonucleotide & RNA	2%	1%	0%	2%	1%
Stem Cell	3%	2%	1%	2%	0%
Carbohydrate	1%	1%	2%	1%	1%
All Other	3%	3%	1%	3%	1%

Source: PharmaCircle Pipeline & Products Intelligence Module (Pipeline Dynamics). The 2021/22 pipeline reflects the pipeline as of March 31, 2021.

The trend toward biologics and macromolecules in the clinic continued in 2021. Throughout the past 6 years, the proportion of small molecule therapeutics in the clinic has dropped from 66% to 49%. Much of this drop can be accounted for by the large number of biologics and macromolecule therapeutics in Phase 1 development. By the time products have reached Phase 3 development, small molecule therapeutics more clearly dominate. The reason could be two-fold, the highly speculative nature of many biological products in early stage clinical development, and/or the development success of dose-modified formulations of existing small molecules, generally later-stage products, targeted to improved clinical benefits or new indications.

The number of cell and gene therapy products in early clinical development continues to surprise. The numbers may well reflect multiple variations of vector and gene constructs being investigated in a variety of indications. The 2021/22 figures are a little bit lower than what was seen with the 2020/21 dataset. The pipeline share of gene and cell therapy products is much lower in later development stages.

For all the excitement surrounding RNA-based therapeutics, these products still represent a small proportion of clinical trial products, on the order of 1 in every 50 products.

The maturity of antibody therapeutics is seen in a consistent share of 11%-14% from Phase 1 through Phase 3. The potential applications and limitations of antibodies are reasonably well understood, which has led to investments in optimizing their presentations, both formulation and device related, to extend their usefulness in the in-patient and out-patient setting.

Cancer continues to be the major focus of pipeline products

Active Clinical Stage Programs by Disease Area, 2015/16 to 2021/22

	2015/16	2021/22	Change	Average Annual Change
Cancer	1,837	3,632	98%	16%
Infectious Disease	996	2,245	125%	21%
CNS	772	1,096	42%	7%
Endocrine/Metabolism	544	663	22%	4%
Inflammation/Immune	538	654	22%	4%
Skin Disorders	361	441	22%	4%
Cardiovascular Diseases	317	370	17%	3%
Pain Management	285	304	7%	1%
Respiratory	255	301	18%	3%
Eye Diseases	192	379	97%	16%
All Other	1,269	1,799	42%	7%
Total	7,366	11,884	61%	10%

Source: PharmaCircle Pipeline & Products Intelligence Module (Pipeline Dynamics). The 2021/22 pipeline reflects the pipeline as of March 31, 2021. (The figures in this table represent programs rather than products. A product may be in development in more than one Disease Area.)

The growth in clinical-stage infectious disease products continues to lead all disease areas, even cancer. The opportunities and needs in infectious disease are driven by new and increasingly resistant viral, bacterial, and fungal targets, best exemplified by COVID-19. While many products may enter the clinic, the attrition rate is very high.

While cancer may have fallen behind infectious diseases in terms of annual growth rate, it stands alone in terms of number of products in clinical development, accounting for 31% of all products. Once again, the needs and opportunities are obvious. What is perhaps unusual is that an increasing number of cancer products in development might well be classified as me-too products pursuing validated therapeutic mechanisms with biologics, often antibodies and small molecules, that struggle to demonstrate meaningful therapeutic improvements. This is an area in which differentiation will depend on providing improved pharmaceutical characteristics possible with drug delivery-, formulation-, and device-based technologies.

The strong growth in the eye diseases clinical pipeline acknowledges the significant expectations of patients and physicians for pharmaceutical solutions to conditions plaguing an increasingly elderly population. The range of products in development include simple reformulations of well-validated actives to provide greater convenience in dosing, through easier patient administration or extended dosing intervals. This is exemplified by products using device-based technologies that can extend dosing intervals of up to 6 months with implants, or as short as a day with drug-releasing contact lenses

The other disease areas show little growth, but that disguises some important new therapeutic treatments for conditions, such as migraine, atopic dermatitis, and asthma, often through unconventional delivery routes.

Clinical stage injectable products continue to take share from other delivery routes

Delivery Route Products as a Share of All Clinical Stage Products, 2021/22

	2015/16	2021/22
Injection	48%	52%
Oral	39%	38%
Topical	6%	4%
Ophthalmic	2%	2%
Inhalation	3%	2%
Nasal	2%	2%
Transdermal	1%	1%

Source: PharmaCircle Pipeline & Products Intelligence Module (Pipeline Dynamics).The 2021/22 pipeline represents the status of the pipeline as of March 31, 2022. (Early stage clinical programs, notably Phase 1, often do not provide information regarding Delivery Route. Products without defined routes are excluded from the analysis.)

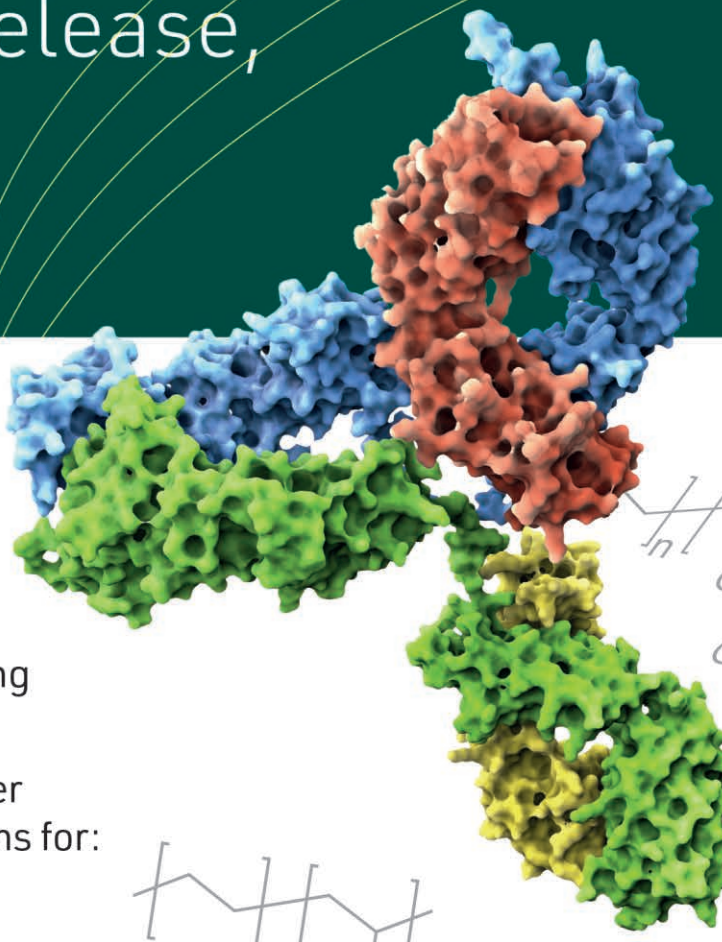
There are few surprises with the latest figures regarding delivery route for clinical-stage products. Cancer and infectious diseases treatments that require more precise dosing adjustments according to weight and body area benefit from the flexibility provided by the injection route. In addition, with the increasing number of macromolecule products in development, there is often no option for delivery beyond injection, whether by the subcutaneous, intramuscular, injection, or infusion routes. The availability of many new device and formulation technologies that can simplify dosing by injection in the clinic and out-patient settings make injection a much more palatable dosing option.

The increased use of the injection route is coming at the expense of most delivery routes other than the oral route. For many indications, oral delivery continues to be the preferred dosing route even for indications such as cancer if it can improve the overall patient experience and reduce service delivery costs without compromising efficacy. For example, the approval of an oral tablet formulation of azacitidine, Onureg (Celgene/Bristol Myers Squibb) can simplify out-patient dosing while avoiding outpatient clinic visits. Improved convenience generally leads to better compliance, which leads to better clinical outcomes.

There are interesting new options being developed for delivery by the nasal and ophthalmic routes. These are generally targeted and don't represent a sufficiently large number of products to be visible with a simple analysis as earlier presented. More detail is available at PharmaCircle LLC.

Sustained Drug Delivery

With controlled-release, patient-centric therapeutics

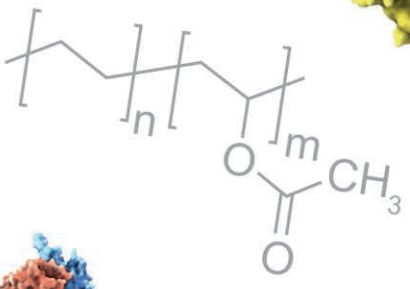


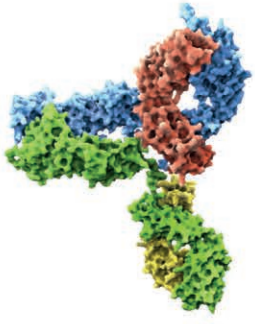
VitalDose® EVA is a copolymer drug-delivery platform providing controlled release through implant and insert dosage forms.

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

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

- Monoclonal antibodies
- Small molecules
- Peptides





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AUTOINJECTOR TECHNOLOGY

De-risking Biosimilar Development With a Clinically Validated & Commercially Proven Disposable Autoinjector

By: Victoria Meyer, MBA

INTRODUCTION

As biosimilar development continues to accelerate with nearly $112 billion in biologic medicines set to lose exclusivity in the global market by 2025, the market is becoming increasingly competitive, putting first-to-market biopharmaceutical companies at a key advantage.[1] With current timelines for biosimilar development and review from health authorities estimated to be nearly 7 years at a cost of between $100 and $300 million to develop, delays during combination product development and regulatory approvals can impact launch timelines and potential market penetration.[2,3] A fundamental area in which biopharmaceutical companies can de-risk the launch process is by choosing a suitable autoinjector technology and partner.

Anticipating and retiring inherent risks in biosimilar development is one of the most essential tasks to be undertaken by companies seeking coveted first-mover status. And yet, the development and commercialization of biologic combination products to treat chronic conditions entails highly complex and challenging processes. Stringent performance requirements, together with increasing regulatory demands and intense competition, contribute to the complexity. Certain factors will be essential in establishing and maintaining an early lead. These include evaluation and selection of suitable combination product technology, and the selection of a combination product development partner with proven commercial solutions, complementary capabilities, and the expertise to positively address those complexities. A solution and partner that can help biopharmaceutical companies manage costs will be essential to achieve commercial success in a market that will only become more competitive. For many biopharmaceutical customers, BD and the BD Physioject™ Disposable Autoinjector have offered the appropriate combination of technology, documentation, and resources required for timely success.[4]

FACTORING IN A RAPID LAUNCH

What factors are evaluated to ensure a fast biosimilar launch? Various internal market research studies undertaken by BD suggest the chosen autoinjector should be a commercially available device that works in conjunction with a commercially available prefillable syringe.[5,6] To limit the possibility of bottlenecks during assembly and production, the device should incorporate a simple design, which aims to limit the steps required for assembly to help streamline the production process. Ensuring that development support is available from the device partner is key. This should include assembly guidance documents as well as compliant documentation for regulatory approval. The ability of the device partner to provide fast access to small quantities of product during the development phase will also help support time to market. The device partner should be able to provide flexible support, including services such as combination product testing, and medical affairs and regulatory support, as required. Addi-

tional factors can include providing product customization options and the ability to meet the customers' cost requirements.

BD PHYSIOJECT™ DISPOSABLE AUTOINJECTOR: ITS MILESTONES CAN STREAMLINE YOUR PATH TO MARKET

With an established track record of delivering medications for more than 10 years, the BD Physioject Disposable Autoinjector has attained some significant milestones. To date, more than 118 million BD Physioject Disposable Autoinjectors have been sold.[7] What's more, when integrated with the BD Hypak™ Glass Prefillable Syringe for Biotech, the BD Physioject Disposable Autoinjector has proven to be a dependable system, with greater than 99.999% reliability linked to system integration.[8] Today, millions of patients and more than 15 pharmaceutical companies benefit from the robust design and manufacturing quality of the BD Physioject Disposable Autoinjector for more than 10 chronic therapeutic indications.

INTEGRATION: ONE-STOP ACCOUNTABILITY FOR PERFORMANCE OF THE TOTAL DELIVERY SYSTEM

A well-integrated system can help mitigate system performance risks early in the combination product development process. The BD approach to integration is behind the success of the BD Physioject Disposable Autoinjector system.* BD ensures components work together, helping avoid integration issues between the drug, the primary container, and the secondary solution, which can delay launch times significantly. The BD approach to integration focuses on ensuring every system component, including the barrel, stopper, needle, needle shield, primary container, and secondary delivery system, is compatible and functions cohesively. This strategy helps to develop a robust delivery system that performs as designed and meets regulatory requirements for safety, effectiveness, functionality, performance, and usability. The hardiness of this approach has proven itself over the course of 118 million autoinjectors sold for chronic applications. The BD approach to integration also means that you will have a single partner that can deliver all components of a drug delivery system, along with system-level documentation and supporting data which, in turn, create a more readily adoptable format for the critical step of combination product regulatory approval.

HUMAN FACTORS STUDIES & RECOGNIZED EASE OF USE

Biosimilars intended for self-injection must demonstrate high levels of patient safety and ease of use while working within the competitive and price pressures specific to the biosimilars market. In its more than 100 years of developing medical technologies to address healthcare challenges, BD has established a patient-centric culture reflected throughout its product design approach. BD conducts human factors engineering testing on its most advanced products across a range of representative users to confirm the integrated devices are safe for use as a system. While biopharmaceutical companies will conduct their own human factors testing with the actual formulation and intended patient population, by leveraging human factors studies in the iterative design of the BD Physioject Disposable Autoinjector, BD provides assurance in the usability of the combined components and reduces the risk of unforeseen issues.

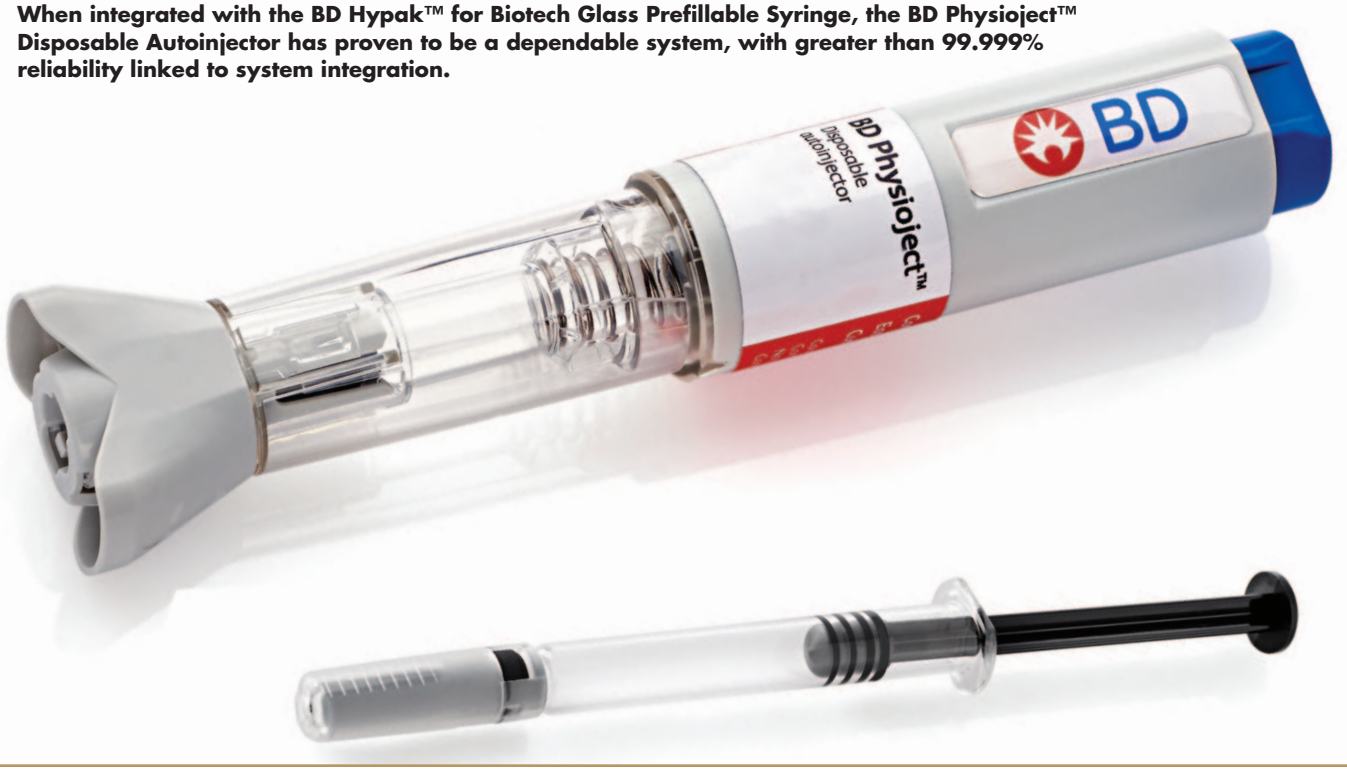
To inform and validate the design of the BD Physioject Disposable Autoinjector, BD conducted nine human factors studies, including seven formative and two summative studies,^^ involving more than 600 individuals.[9-11] In these studies, BD examined all aspects of performance, safety, ef-

FIGURE 1

The BD Physioject™ Disposable Autoinjector features a large window with a 360 degree view of the drug inside, one-button activation, and customizable attributes including button and cap color.

FIGURE 2

The BD Physioject™ Disposable Autoinjector is a commercially proven, three-step disposable autoinjector. When integrated with the BD Hypak™ for Biotech Glass Prefillable Syringe, the BD Physioject™ Disposable Autoinjector has proven to be a dependable system, with greater than 99.999% reliability linked to system integration.



ficiency, patient acceptance, and ease of use, including pain perception compared with the use of stand-alone prefilled syringes.[9‡] This work generated essential insights regarding the overall user-product interface and demonstrated patients' positive response and acceptability of both the product design and the user experience.

This emphasis on human factors led to a patient-centric design and the incorporation of a robust integrated passive sharps injury protection feature. In human factors and clinical studies with over 1,300 simulated injections, the needle covering system integrated in the BD Physioject Disposable Autoinjector automatically deployed and locked in 100% of cases.[9,10^∞] The BD Physioject Disposable Autoinjector also incorporates a patient-centric design that allows the patient to control the start of the injection once the autoinjector is placed on the skin and the cap is removed. In a human factors study, 90.8% of patients with rheumatoid arthritis found that the force required to press the button was acceptable and 81.5% of patients found that the three-step injection process with the BD Physioject Disposable Autoinjector was simple.[10§¶]

Specific design features include:

- Demonstrated patient usability and ease of use, especially in patients with limited dexterity eg, patients with rheumatoid arthritis[10,12]
- A 360° view of the drug and injection process, allowing 100% drug visibility
- A simple, one-touch injection button for activation[10]
- A hidden needle before and during injection, which aims to help reduce needle-stick anxiety[13-15]
- A protected needle before and after injection, which aims to help limit the risk of needle stick injury[13-15]
- A cap designed to prevent re-capping once the device has been opened[13]
- Two subassembly components, which aim to limit the steps required for assembly[13]

The patient-centric design of the BD Physioject Disposable Autoinjector was recognized in 2015 with the Ease of Use Award from the Arthritis Foundation.[16]

DOCUMENTATION

BD Physioject Disposable Autoinjector comes with full, supportive data packages of system performance to help de-risk development and support time to market. Documentation and support provided with the BD Physioject Disposable Autoinjector include:

FIGURE 3

To inform and validate the patient-centric design of the BD Physioject™ Disposable Autoinjector, BD conducted nine human factors studies, including seven formative and two summative studies, involving over 600 individuals.^^ Today, millions of patients and more than 15 pharmaceutical companies benefit from the robust design and manufacturing quality of the BD Physioject Disposable Autoinjector for more than 10 chronic therapeutic indications.

- Customer product specifications
- Customer drawings
- BD Design Verification Summary Report and test methods
- ISO10993 compliance statement
- Materials of concern and safety information
- Intended use and residual risk analysis statements
- Final assembly recommendations
- BD Physioject Disposable Autoinjector validated direction for use (DFU)#
- Human Factors Engineering summary report
- List of machine manufacturers for final assembly
- Letter or Authorization (LOA) for Master Files and technical dossier
- ISO-11608 compliance quality statement

FAST ACCESS TO SAMPLES

BD provides fast access to samples for clinical use through the BD PartnerPath™ Program to ensure flexibility in supply and support time to market. The BD PartnerPath Program is for anyone with a drug in development requiring access to low quantities of product quickly. For this reason, BD can ensure availability for a multitude of products including primary containers, plunger stoppers, plastics components, and secondary devices, within 12 weeks.

THE BD PREFILLABLE SYRINGE – AT THE HEART OF DE-RISKED SYSTEM INTEGRATION

Since 2014 more than 3.9 billion BD Glass Prefillable Syringes have been sold to support the delivery of injectable biotech drugs.[17] BD Physioject Disposable Autoinjectors are fully integrated with the BD Hypak™ for Biotech Glass Prefillable Syringe and fully compatible with the BD Neopak™ Glass Prefillable Syringe.

The BD Hypak™ for Biotech Glass

Prefillable Syringe is a fully integrated Prefillable Syringe and key component in the more than 10-year success and track record for reliability of the BD Physioject Disposable Autoinjector. The BD Hypak for Biotech Glass Prefillable Syringe is a commercially proven, sterile, clean and ready-to-fill (BD SCF™) syringe barrel container featuring key compatibility factors for biotech drug delivery. It offers limited reject rates on customer process through fewer visual/cosmetic defects, and improved drug compatibility through specified low tungsten residue levels.[18-19†] Its controlled Length Under Flange and gliding specifications are the foundation of its compatibility with the BD Physioject Disposable Autoinjector.[19]

The BD Neopak™ Glass Prefillable Syringe platform has been developed leveraging the expertise and experience BD has acquired during its more than 30 years of collaboration with the biopharmaceutical industry.[20] The BD Neopak Glass Prefillable Syringe platform is designed to address key needs of biotech manufacturers such as drug and autoinjector compatibly.[21,23] Fully compatible with the BD Physioject Disposable Autoinjector, the BD Neopak 1 mlL Glass Prefillable Syringe features increased resistance to breakage, specified low and ultra-low tungsten residual levels, and reduced silicone quantity aiming to support reliable performance.[22,23††]

SERVICES TAILORED TO SUPPORT YOUR COMBINATION PRODUCT DEVELOPMENT JOURNEY

To every partnership, BD offers a range of end-to-end services based on experience in designing and integrating components into systems and extensive collaboration with drug developers and biosimilar manufacturers. These services are designed to help biopharmaceutical partners choose the correct components and systems for their applications, to assess and offer solutions to any potential challenges or sensitivities, and to help produce the necessary data packages needed to demonstrate the safety and performance of the integrated combination product. These services include the following:

- Analytical and bioanalytical chemistry capabilities
- Formulation services
- Functional and performance testing
- Clinical/human factors consultancy
- Combination product documentation support and testing
- Process consultancy
- Regulatory support

Combination product support occurs throughout the development process, from matching the right set of components with the formulation in Phases 1 and 2, to validation testing of the system in Phases 2 and 3. BD offers this breadth of capabilities in combination with the entire system of components to enable customers to anticipate and resolve challenges before they become issues from a system performance perspective.

SUMMARY

Depth of in-market experience with primary containers and secondary solutions, confirmed rigor in product development processes informed by more than 30 years of expertise in injection science and translational research, and an extensive global manufacturing network, are advantages BD can offer as a partner. BD leverages these assets to develop innovative solutions that provide peace of mind for customers and contribute to patient well-being, and de-risked combination product development and commercialization. For these reasons, the BD Physioject Disposable Autoinjector has been chosen by biopharmaceutical customers developing new biologics or biosimilars in 1mL applications. ◆

*When integrated with BD Hypak™ for Biotech Glass Prefillable Syringe

†As compared to BD Hypak Prefillables Glass Syringes

††As compared to BD Hypak™ for Biotech Glass Prefillable Syringe

**A number of services can be provided at an additional cost

‡In a clinical study with 40 healthy volunteers, at the end of the last session, subjects were told they will have an unscheduled additional injection. The results showed that all 40 subjects (100%) preferred the BD Physioject™ Disposable Autoinjector for that injection (which was

not done, the question was solely for informational purposes).

^In a human factors study with 65 patients with rheumatoid arthritis, 100% (n=390/390 injections) of passive sharp injury prevention feature activation was recorded.

∞ In a clinical study with 40 healthy volunteers, the passive sharp injury prevention feature activation was recorded 100% (n=480/480 injections) of the time.

§* In a human factors study with 65 patients with rheumatoid arthritis, after 6 simulated injections, n=59/65 (90.8%) of patients with rheumatoid arthritis gave a score ≥6 on a 0-10 Likert scale for acceptance of further self-injections with BD Physioject™ Disposable Autoinjector.

¶ In a human factors study with 65 patients with rheumatoid arthritis, after 6 simulated injections, the mean acceptance for the 3-step injection process (perceived required force to press the button, force to maintain the device on skin and perceived visibility of the move of the stopper during the injection) was 81.5% where patients with rheumatoid arthritis gave a score ≥6 on a 0-10 Likert scale.

Directions for Use (DFU) are provided to support development of the instructions for use (IFU)

^ ^Between 2005 and 2010, BD conducted 7 formative and 2 summative studies, involving over 600 individuals

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BIOGRAPHY

Victoria Meyer has worked at BD for more than 14 years across several business units in various commercial roles, including sales, sales operations, and regional marketing. She is currently the Senior Global Strategic Marketing Manager responsible for leading 1 mL product platforms across the BD Biologics Portfolio. In this role, she closely partners with Research & Development and other cross functional teams to define, develop, and deliver programs, data sets, and system solutions to pharmaceutical customers to help support combination product development. She earned her MBA from Columbia Business School and her undergraduate degree in Economics from the College of the Holy Cross.

BIORESORBABLE POLYMERIC MATRICES

Convergence of Materials Science & Drug Development to Treat Challenging ENT Diseases

By: Maria Palasis, PhD, and Robert Kern, MD

INTRODUCTION

Sustained and controlled delivery of medicine offers important benefits in terms of longer duration of action, reduced dosing frequency, and improved patient comfort and compliance. Several strategies are available to modify release of active substances with a goal of improving patient outcomes; however, these strategies are not applicable to all diseases or areas of the body for delivery, leaving significant unmet needs. For example, it has been challenging to achieve local therapeutic action at tissues deep in the ear, nose, and throat (ENT) passages where inflammation and infection are the drivers of chronic symptoms.

Polymeric microspheres have been used for years for controlled delivery because of their ability to encapsulate different types of drugs, biocompatibility, high bioavailability, and sustained drug release characteristics.[1] While microspheres remain an important option for sustained delivery, therapeutic applications are limited to those requiring systemic distribution of the drug. Strategies to localize sustained drug release include the use of foams impregnated with drug product. An example of this approach is a foam-based extended-release formulation of ciprofloxacin for use in ear infections.[2] While this once-daily dosing of foam eliminates the need for multiple doses of messy ear drops, use of foams has not been demonstrated to achieve long-term delivery of a therapeutic to a target organ.

Drug-eluting stents (DESs) are drug-device combinations deployed to localize drug delivery in the treatment of obstructive arterial disease. These stents consist of three main parts: a metallic platform, a polymeric coating, and an active pharmaceutical agent incorporated into the coating.[3] High rates of in-stent restenosis associated with bare-metal stents led to development of DESs, which were designed to mitigate the injury created by implantation of the stent.[4] In other words, the goal of the drug in DESs is to make the device – the stent – work better.

As our research team explored ways to deliver drugs and treat disease in a targeted, long-term manner for specific ENT conditions, we sought to move beyond the limitations imposed by technologies such as microcarriers and foams. At the same time, we envisioned an approach that was, in essence, the reverse of a DES. We didn't look for a drug to make an existing device better, rather, we wanted to develop an implantable material with a specific set of characteristics that offered the potential to make a broad range of therapeutics more effective.

We ultimately found a unique way to solve a unique problem at the intersection of material science and drug formulation chemistry.

CHECKING ALL THE BOXES

When considering an advanced material and design for an implant capable of localized, long-term delivery of a therapeutic, the list of prerequisites is lengthy. As a starting point, we considered the nature of the soft tissues we would be targeting and knew the implants needed to mimic the strength and elasticity of the native tissue and also have shape-memory properties. These features would allow the implant, and hence the drug, to remain in contact with the tissue surface even as the tissue changes and remodels. The implant material also had to be resorbable and biocompatible.

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WE CARE

Development of a shape-memory material that is also bioresorbable required a unique composite design as existing approaches offered limited strength. The bioresorbable, composite polymeric implants with shape-memory properties that Lyra has developed are described in Nature Materials.[5]

The shape-memory matrix consists of variants of poly(glycolic) acid that are braided and coated with a crosslinked elastomer of poly(glycolide-co-caprolactone). The elastomer coating delivers higher mechanical strength in terms of compression, expansion, and elasticity compared to braids without the coating. The elastomer is cured on the braid at the fully expanded diameter, providing a mechanism for the implant to self-expand to its fabricated diameter by constraining the points of intersection of the braid. The scaffolds were shown to be biocompatible and highly resorbable in animal studies.

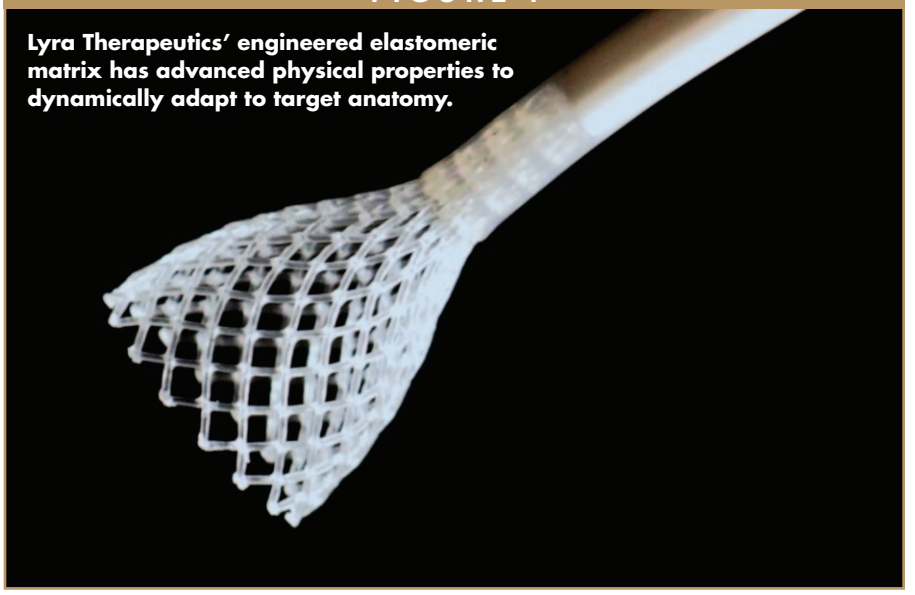
This novel approach to coupling strong materials with elastomeric, shape-memory materials opened the opportunity for the long-term targeted delivery of drugs via bioresorbable constructs that mimic the properties of native soft tissue.

THERAPEUTIC APPLICATIONS

At Lyra Therapeutics, we have integrated this technology based on advanced materials science with extensive expertise in drug development and formulation chemistry to create our XTreo™ platform. Foundational components of the XTreo platform are outlined below.

A **biocompatible mesh design** optimizes surface area for drug release while maintaining underlying tissue function through an open cell design. The mesh is composed of bioresorbable polymers that are pliable to maximize patient comfort.

FIGURE 1



Lyra Therapeutics' engineered elastomeric matrix has advanced physical properties to dynamically adapt to target anatomy.

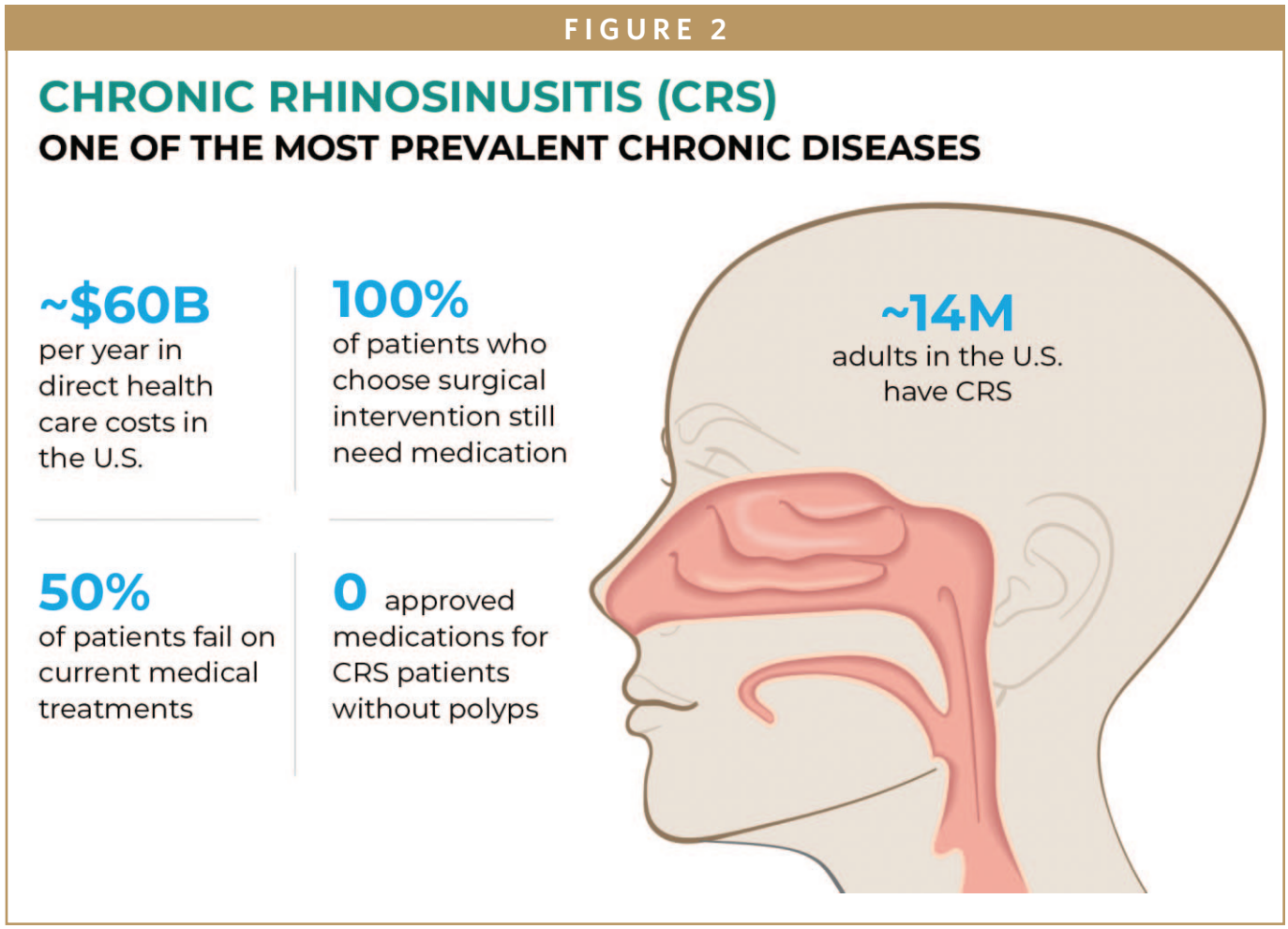
An **engineered elastomeric matrix** (Figure 1) dynamically adapts to target anatomy. Adaptive elastic tension gives it shape-memory to resist deformation, which is essential for ensuring persistent positioning in the target location. The elastomeric matrix works in conjunction with the underlying mesh to exert out- ward pressure at the target location, keeping it in place as tissue remodels. Resorption of the matrix can be con- trolled to effectively tailor the therapeutic to different indications; it can be designed to remain intact or be resorbed within a specific time period. A fine-tuning process effectively balances the pace of resorption and self-expansion.

A **versatile polymer-drug complex** is potentially amenable to continuous, prolonged drug release across a wide range of drugs for different therapeutic applications. With proprietary bioresorbable polymer-drug formulations, the platform can be used to customize the controlled-release of drugs for many chronic diseases.Our current pipeline of therapeutics target tissues deep in the ear, nose, and throat (ENT) passages and are designed to deliver continuous drug therapy for up to 6 months following a single non-invasive, in-office administration.

TARGETING CHRONIC RHINOSINUSITIS

Selection of chronic rhinosinusitis (CRS) as our first indication was driven by significant unmet clinical need (Figure 2). CRS is one of the most prevalent chronic diseases, affecting at least 14 million in the US alone.[6] CRS is diagnosed after persistent and severe symptoms, which include nasal congestion, drainage, reduced or lost sense of smell, and facial pain and pressure, have persisted for 3 months or more. CRS symptoms can lead to sleep disturbances, daytime fatigue, depression, and anxiety, severely impacting a person's well-being and quality of life, both personally and professionally. A typical CRS sufferer misses 18 workdays per year, has a 36% reduction in on-the-job effectiveness,

FIGURE 2



suffers a 38% loss of productivity, and often withdraws from daily personal activities.[7]

Conventional CRS treatments are intended to reduce mucosal swelling resulting from underlying inflammation, reduce existing nasal polyps and promote sinus drainage. CRS sufferers typically start with over-the-counter remedies and if those don't work, may move to a topical intranasal or oral corticosteroids. Topical nasal steroid sprays are not designed to reach the site of inflammation deep within the nasal passages, and systemic exposure to oral steroids also presents safety concerns for these patients.

About 10% of CRS patients develop nasal polyps, which are benign, tear-shaped masses that form in sinus cavities. Currently, there are no FDA approved drug therapies for the 90% of CRS patients who do not have polyps.

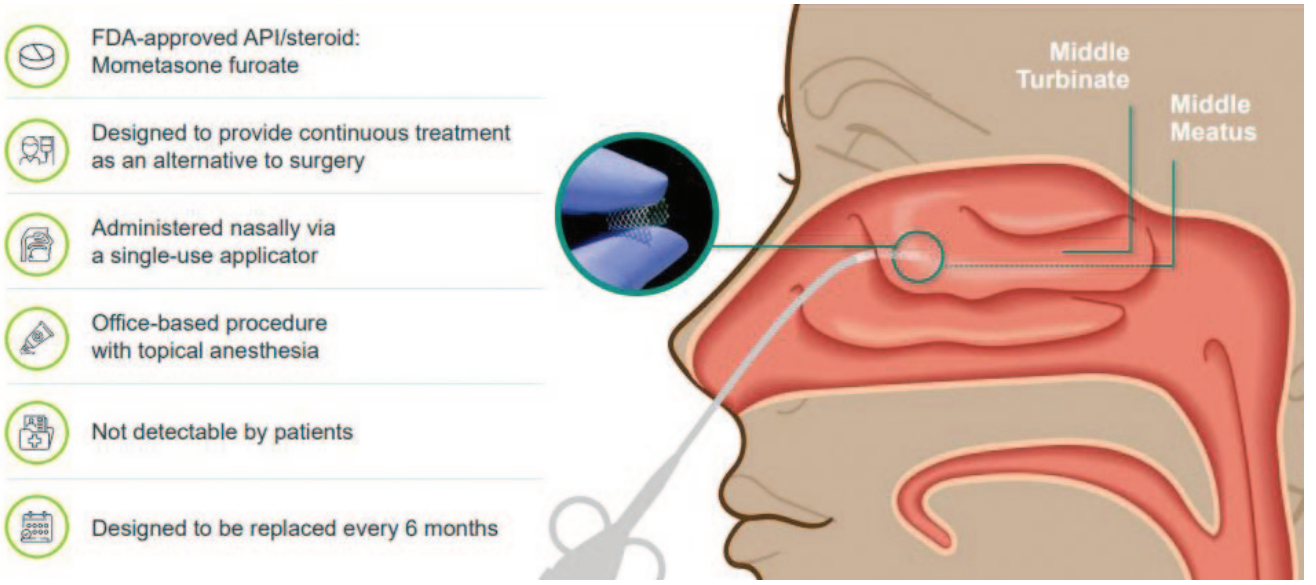
Overall, 50% of the 8 million CRS patients in the US fail attempts to manage CRS with medication.[8] These patients may be referred for sinus surgery, which can be costly and uncomfortable. A small minority of patients proceed with sinus surgery, and those that do often require follow-up revision surgeries. The majority of CRS patients still require medical management after surgery.

The unmet need in CRS is significant as none of the current treatment options offer the sustained solution required for long term management of this disease.

LYR-210 is an anti-inflammatory implantable drug matrix based on our XTreo platform designed to deliver mometasone furoate, a potent anti-inflammatory agent, consistently and locally to the inflamed mucosal tissue of patients with CRS for up to 6 months from a single treatment (Figure 3).

In the Phase 2 LANTERN study, LYR-210 demonstrated rapid and durable improvements in symptom severity for patients both with and without nasal polyps after a single administration. At 4 weeks, 70% of patients showed clinically meaningful improvement, and by 24 weeks 100% of patients achieved meaningful symptom improvement. Furthermore, approximately 50% of CRS patients treated with LYR-210 experienced durable symptom improvement 6 months after removal of the matrix. The lack of a strong rebound in CRS symptoms post-treatment after removal of the matrix may indicate the potential for longer-term benefit for

FIGURE 3



LYR-210 is designed to be the gold standard for treatment of CRS. It is the only product candidate designed to provide 6 months of CRS therapy with a single treatment.

some patients.

Another long-acting anti-inflammatory implantable drug matrix, LYR-220, is in development for CRS patients who have undergone a prior sinus surgery but continue to have persistent disease. Sinus surgery results in an enlarged nasal cavity, and LYR-220 employs an oversized matrix to ensure a proper fit.

An applicator designed for the specialized biology and contour of the ENT space is used by the physician to administer LYR-210 and LYR-220 in a fast, non-invasive, in-office procedure. The flexible matrix maintains maximal contact with the irregular sinonasal anatomy and dynamically expands to the target anatomy, promoting continuous apposition to the surrounding mucosa for efficient and consistent local corticosteroid delivery while being unobtrusive to patients.

SUMMARY

The XTreo platform represents a unique and powerful convergence of materials science, drug development, and formulation chemistry, enabling the local delivery of medication to anatomical spaces not accessible by conventional therapeutic approaches. The remarkable flexibility of the platform opens possibilities to explore additional indications within the ENT space, such as allergic rhinitis, olfactory dysfunction, ear conditions, and sinus-related rare disorders. Because this versatile platform enables modification of the form factor, the drug and its elution profile, we can explore indications beyond the ENT space as well, such as nasal delivery for CNS disorders. Lyra's XTreo platform has potential in a number of indications where long-term delivery would improve local bioavailability and enhance efficacy and safety. ◆

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BIOGRAPHIES

Dr. Maria Palasis is President and Chief Executive Officer of Lyra Therapeutics. She is an accomplished scientist, inventor, entrepreneur, and healthcare industry leader who has led the development of multiple highly successful medical device and drug delivery systems. She is considered one of the pioneers of drug-eluting stents, currently over a ~$6B annual commercial market, and she led Lyra through its successful initial public offering in May 2020 – one of the first IPOs after lockdown for the COVID-19 pandemic. She was elected into the National Academy of Engineering for outstanding contributions to the design of medical devices and drug delivery systems, including her work on LYR-210 and LYR-220. She earned her PhD in Chemical Engineering from the University of Cincinnati, Collge of Engineering & Applied Science.

Dr. Robert Kern is Chief Medical Officer of Lyra Therapeutics and the George A. Sisson Professor and Chair, Department of Otolaryngology – Head and Neck Surgery, Northwestern University Feinberg School of Medicine. He has 30 years of experience in the ear, nose, and throat field and is a practicing otolaryngologist with a subspecialty interest in rhinology. He is the immediate Past President of the American Rhinologic Society and current President of the International Society of Inflammation and Allergy of the Nose.

Drug Development
EXECUTIVE

Marc Sauer, PhD
Chief Science Officer
BIOVECTRA

BIOVECTRA: mRNA & the Future of Pharma

When Dr. Marc Sauer joined BIOVECTRA as a research scientist in 2006, the company of 60 was focused on small molecules and microbial fermentation. Today, at just shy of 600 employees, BIOVECTRA is a global CDMO positioned to serve pharmaceutical companies in the post-pandemic era of mRNA vaccines, therapeutics, and personalized medicine. Backed by a supportive culture, a strong team, and a location that allows for close partnerships with clients across the world, the future looks bright for BIOVECTRA and its new Chief Science Officer, Dr. Sauer.

Drug Development & Delivery recently spoke with Dr. Sauer about his new position, growth at BIOVECTRA, and how he believes mRNA technologies can best be leveraged to improve the lives of patients.

Q: You were recently named the first Chief Science Officer at BIOVECTRA. What was behind that move, and what are your goals in this new role?

A: The creation of this new role reflects the company's mission to not just advance our science program but to truly provide a seamless experience for our clients and partners by combining our scientific competencies under a single umbrella. BIOVECTRA has been serving pharma for more than 50 years, having started in small molecules and diagnostic reagents. Today, as a global CDMO, we offer cutting-edge technologies and end-to-end experiences to our clients for small and large molecules, complex chemistry, biologics, and soon, plasmid DNA and mRNA therapeutics. As we onboard these new capabilities, BIOVECTRA wants to ensure we can continue to offer the experience and responsiveness that our customers expect from us.

My initial focus as CSO is to create an integrated, one-stop shop for tech transfer, process development, and scale-up by bringing all science activities together into one office. This includes chemistry, biologics, analytical and formulation process science with manufacturing science and technologies. Our clients will be able to work with my team from quotation, to clinical development, to commercial manufacturing for their projects, ensuring complete knowledge transfer

along the way.

My tenure at BIOVECTRA has prepared me well for this. I'm a chemist by training, completing my PhD in Physical Chemistry at the University of Basel in Switzerland. I have more than 20 years of pharma experience in both Europe and North America and have been with BIOVECTRA for more than 16 years. I started as a research scientist and quickly moved into leadership positions in analytical development and quality before spending 6 years as Head of Quality Control. Eight years ago, I was named VP of R&D/General Manager, and now Chief Science Officer.

Q: BIOVECTRA has made several major investments lately. Can you tell us what's been happening and why?

A: We're building and expanding quite significantly at the moment. In 2014, we acquired a new facility in Nova Scotia that has become a dedicated headquarters for biologics with large-scale commercial bioreactor capacity ranging from 3,000-17,000 liters. We've partnered with ABEC, who designed, manufactured, and are currently installing a 100-1,000-liter single-use microbial fermentation suite at the site. This will give our customers greater flexibility, faster turnaround, and higher capacity utilization.

Our new biomanufacturing and mRNA vaccine expansion in Charlottetown broke ground in April of this year. This is a $79.6 million expansion that will enable us to produce up to 160 million doses of mRNA vaccines per year and prepare and package 70 million fill-finish doses per year for commercial distribution.

In addition, we just recently signed the lease for a 32,000-sq-ft facility in Halifax, which will become our process development and testing Center of Excellence for biologics, plasmid DNA, and mRNA, including cell line development.

There's a lot happening, and it's very exciting to see BIOVECTRA expand and build upon what we've been offering for the past 50 years. Our new capabilities and scale will add more value to our client relationships, allowing us to become an even better partner.

Q: You were remarkably well-positioned for working with mRNA just as the COVID-19 pandemic shined a light on its capabilities. How were you focused on mRNA prior to COVID?

A: As a company, our focus was always on growing our capabilities in an adjacent matter, looking at how to build upon what we already do and know. In our early days, we focused on providing diagnostic reagents and enzymes before moving into regulatory starting materials and active pharmaceutical ingredients. In the early 2000s, we added microbial fermentation to our offering, as well as highly potent APIs and pegylation reagents. As time went on, we began focusing on biologics and complex small molecules.

We've certainly evolved and expanded our scientific capabilities throughout the years, and the unfortunate pandemic offered us an opportunity to pursue plasmid DNA and mRNA.

Even though this is a new direction for us as a company, it's not completely foreign territory to us. Moving into pDNA makes a lot of sense for us, given the history we have in microbial fermentation. We're building upon the capacity we already have and developing the capabilities we've built throughout the past 5 decades in this space. Rather than a big leap into the unknown, we're simply shifting into adjacent fields that make sense for us as a company.

Q: Now that mRNA is more mainstream, how are you able to help pharmaceutical clients leverage this technology?

A: This direction into plasmid DNA and mRNA has absolutely been fueled by the pandemic. Even though mRNA has been around for 10-15 years, it never quite made it into the mainstream. But since COVID, mRNA has piqued the interest of a lot of companies and people in this field.

Now that we're developing pDNA and mRNA capabilities through our Charlottetown expansion, we have several avenues available to continue supporting our clients, and the patients they serve, as the industry evolves. We are positioned to support programs from the clinical stages to commercial manufacturing for mRNA/pDNA vaccines and therapeutics for large patient populations or personalized medicine applications. I truly believe mRNA vaccines are going to be a transformative change within pharma. It's going to completely shift how we envision pharmaceutical manufacturing and combating diseases in the future. It has the potential and power to change the therapeutic landscape of personalized medicine, which will be revolutionary in the medical and pharmaceutical space.

This expansion will also introduce fill-finish to the organization. We've been manufacturing APIs for a long time, but with this expansion and our new capability to produce finished products, we're now entering the manufacturing of drug products — at significant scale.

Q: Supply chain is on everyone's mind; how are you able to help secure your customers' supply chain, and how are you securing yours?

A: It's certainly true everyone has been impacted by supply chain issues these past couple of years. In our industry in particular, the need to produce RNA therapies urgently and at a global scale combined with the overall impact the pandemic had on manufacturing and shipping goods worldwide has put a significant strain on raw materials and consumable items.

As a company, our biggest advantage when it comes to supply chain challenges is our depth of experience. We've been in this business for 50 years and have a wide network of relationships inside the industry.

During the pandemic, we made the strategic decision to partner with ABEC to manufacture our 100-1,000-liter single-use bioreactor technology. As a result of this partnership, BIOVECTRA will be the first CDMO in North America to have the 1,000-L scale of single-use bioreactor technology available.

Our ability to predict and plan for what's around the corner has been a significant advantage. We have a dedicated procurement team working on securing everything we need to carry out each of our initiatives, building inventory for critical projects ahead of time and taking full advantage of dual sourcing opportunities.

Although overall our industry struggled with delays, the strength and breadth of our relationships came to our aid, and we certainly haven't lost any business because of supply chain challenges – we've grown.

Q: BIOVECTRA's message is "We Care." Why is that important to BIOVECTRA and, importantly, to your customers?

A: Throughout my time at BIOVECTRA, we've experienced changes in ownership, engaged in multiple new competencies with our client offerings, and grown our team ten-fold. Right now, we have something in the range of 100 active clients, coast-to-coast across North America, Europe, and Asia. We're truly a global company, but the one thing I always appreciate about BIOVECTRA is how much our people care.

We incorporated this sentiment officially into our corporate identity because we truly are people who care. We care for the products we make, the work we do, and for our colleagues. What stands out in our employee interviews is how much people appreciate the BIOVECTRA community, and that's something we've managed to maintain, despite our tremendous growth. Our employees still support each other, and that is reflected in the quality of the services we provide to our clients and their patients.

Recently, we were named one of Canada's Top 100 Employers because we put action behind this idea of caring for our employees. We are continuously shaping our positive workplace culture, investing in employee development, ensuring we offer employees competitive benefits packages, and donating to causes employees care about.

But what really differentiates us in the marketplace is the way this sentiment extends to our client relationships. We don't position ourselves as just a supplier to our clients – we're a partner. We're focused on seeing them all the way through from early clinical development, through the clinical scales, into commercial manufacturing. We really believe in our partnerships, and we know working closely with our clients over the long term is much more rewarding than simply servicing them as a supplier.

Q: How is your Atlantic Canada location beneficial to customers?

A: It may appear an unusual location for a CDMO. Prince Edward Island (PEI) is the smallest province in Canada; Charlottetown is a smaller city. And our facility in Windsor, Nova Scotia is also not what you'd consider a traditional pharma hotspot. In fact, BIOVECTRA was initially started in the 1970s by a local Dean of Science on PEI to offer job opportunities to local chemistry graduates.

But as it turns out, our location has become one of our biggest advantages. We're closely connected to several major biomanufacturing hotspots like Boston, for example. We're only a 4-hour time difference from the UK, 5 hours from Europe, and 4 hours from the Pacific Coast. This means we're fairly centrally located in terms of where we operate as a company, which is mainly in North America and Europe.

As a Canadian company, we've also developed a public/private partnership with the Canadian government and are part of the national response to improve domestic biomanufacturing capacity. This past November, we announced with both the federal and provincial governments a $79.6-million investment to expand into mRNA vaccine production and to construct a new biomanufacturing facility. Through this partnership, not only are we expanding our offering to clients, but BIOVECTRA is also part of a national solution to ensure the country is better prepared for future pandemics and health emergencies. ◆

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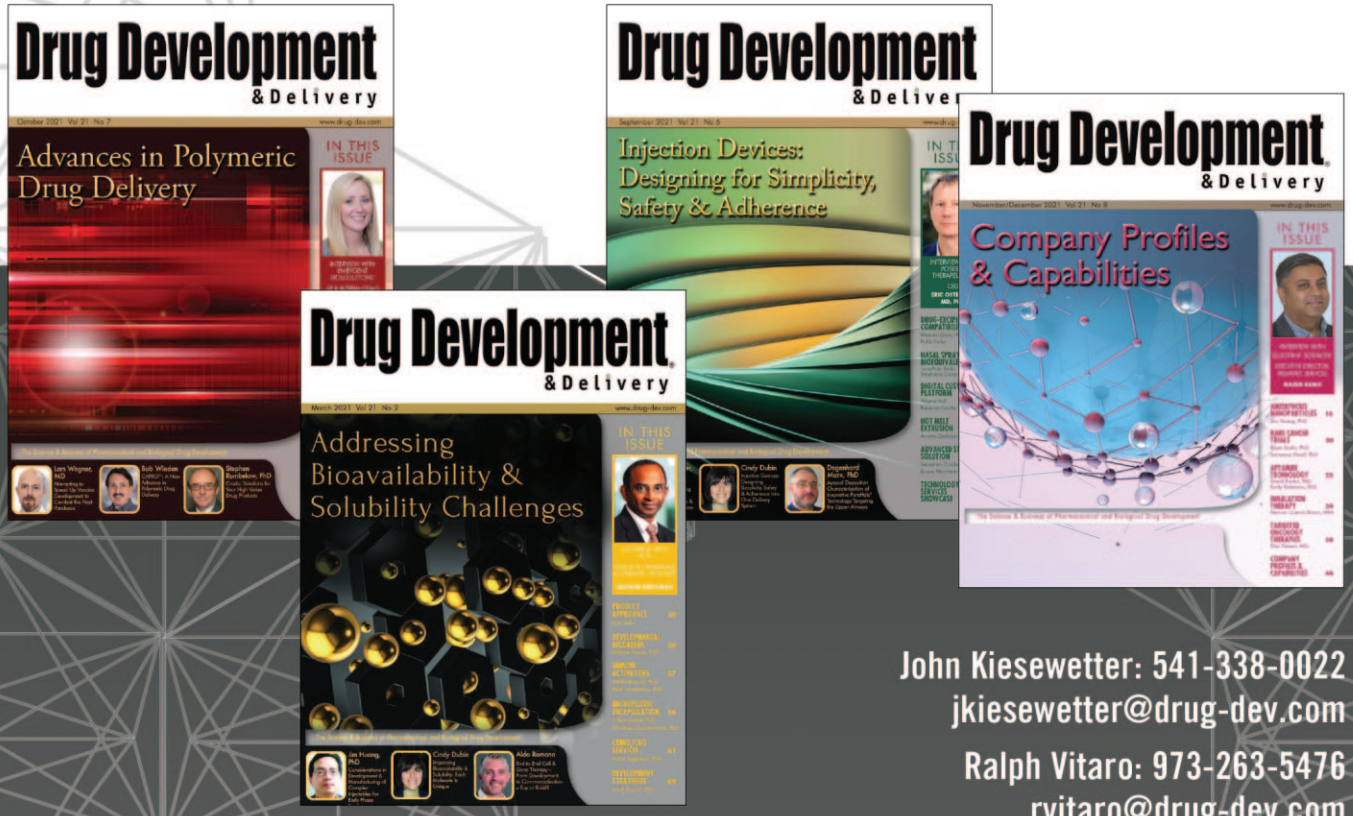

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Special Feature

Outsourcing Formulation Development & Manufacturing: Understanding Critical Attributes Earlier in Development Leads to a More Robust Drug Product

By: Cindy H. Dubin, Contributor

Formulation development and manufacturing outsourcing compresses timelines and mitigates risk, enticing many pharmaceutical and biotech companies worldwide to partner with outsourcing service providers in the early phases of the drug development process. This has resulted in an economic impact on the global formulation development outsourcing market, which is expected to reach a value of $31.8 billion by 2027, up from $21.1 billion in 2021.[1]

A contract development and manufacturing organization (CDMO) able to provide services from early-stage clinical development through to clinical and commercial manufacturing and packaging, with full analytical support, launch capabilities and final distribution, is an attractive proposition," says Jeff Clement, Executive Director, CDMO Business Development North America at PCI.

Pharmaceutical product is loaded into a pharmaceutical coating machine at Almac Pharma Services.

"It is our experience that pharmaceutical and biotechnology companies worldwide are partnering with outsourcing services in early phases of drug product development," agrees Dr. Tom Tice, Senior Director Global Technical Marketing, Evonik Health Care. "For example, small startup companies prefer to do very early-stage research themselves by working from seed money and grant funding. This gives them better innovation control. Then, at a critical point, with data and background intellectual property in hand, and only laboratory-scale processing, they outsource to take their development to the next level. This level is used to improve product characteristics and performance and to bring in a manufacturing process that can be scaled up for GMP manufacturing – a key milestone for product success."

In addition to relying on CDMOs earlier in drug development, pharma is looking to outsource providers to manage timelines and navigate supply chains fraught with material shortages. "The COVID-19 pandemic has undoubtedly led to some reflection after observing how long-established development timelines were successfully challenged in accelerating therapies though development, registration, and in some cases, successful commercialization," says James Hurst, Vice President Operations & Charnwood Site Head, Almac Pharma Services. "Managing development activities to compressed timelines, identification, and timely resolution of development challenges, as well as alignment of the various elements in the supply chain, has never been more important. This is leading to more competition amongst sponsor companies for access to external capacity and capabilities at CDMOs as they look to manage these pressures and access resources to progress their pipelines."

"Clients need to ensure they partner with a CDMO that has a good awareness of both material supplier lead times, availability of alternate merchants, and who have the expertise to offer up viable alternatives that would not impact the performance of the end product," says Helen Baker, Director, Pharmaceutical Sciences, Quotient Sciences. "A CDMO capable of both preempting and adapting to supply chain issues, while maintaining the integrity of a comprehensive and thorough development plan will be most attractive to pharmaceutical clients."

The pandemic also forced the industry to pivot toward new therapeutics, particularly mRNA-based drugs. As a result, many CDMOs have invested in new facilities and state-of-the art equipment focused on biologics manufacturing.

This annual, exclusive *Drug Development & Delivery* report describes how drug sponsors and CDMOs are collaborating earlier, highlights how third-party contractors are navigating material shortages, and discusses how the industry is shifting to address different therapeutic targets and molecules, such as mRNA.

Adare: Addressing Unexpected Challenges

Outsourcing is a good way for pharma and biotech companies developing their pipelines to accelerate time to market because the CDMO has already invested in the facilities and approvals needed to begin work. CDMOs provide their customers with regulatory-approved facilities and highly experienced scientific staff, which can help accelerate times and address challenges that arise.

Adare's expertise proved successful for one client that faced the challenge of an out-of-specification fill weight variation during an encapsulation process, explains Anthony Qu, Chief Technology Officer at Adare. "Early in the project, our client decided to use a small-scale encapsulator to reduce product lost, with a minimum submission batch size," he says. "When manufacturing confirmation batches, we started encapsulating using a Zanasi 40E (not equipped with a vacuum chamber), and we observed large weight variations when encapsulating all the strengths."

The Adare team recognized that because the product is sensitive to the manufacturing process, an encapsulator equipped with a vacuum chamber would significantly reduce the weight variation. "The client agreed with our team's suggestion to switch to a production-scale encapsulator equipped with a vacuum chamber, and thereafter the confirmation batches and submission batches at every strength were successfully encapsulated with

an insignificant capsule weight variation," says Mr. Qu.

Almac: Making Investments and Re-engineering to Support Small & Big Pharma

Outsourcing early development activities is something Almac is experiencing more of as companies look to accelerate from candidate selection to clinical trial entry and ultimately get to proof-of-concept as quickly and efficiently as possible. "Smaller, virtual companies have outsourced these activities for many years, but we increasingly see larger pharma companies outsourcing more of their early development portfolios," says James Hurst, Vice President Operations & Charnwood Site Head, Almac Pharma Services. "Some of these larger companies are pursuing 'reserved capacity models' to guarantee access to formulation, analytical, and manufacturing capabilities and capacity so that they can move multiple assets in their portfolios forward quickly when the need arises."

The Almac Group made investments in cold-chain storage, packaging, and distribution capabilities to support the clinical supply chain for numerous mRNA vaccines during the COVID pandemic. "We also support elements of the clinical and commercial supply chain for a considerable number of cell and gene therapies aimed at niche indications, small patient populations, and small production volumes," he says. "We have re-engineered internal processes from order receipt to production, release and dispatch, to enable incredibly fast turnaround times for products that are often life-altering or lifesaving."

For example, one client was approaching the successful launch an adult dosage treatment, but had a late change in direction regarding the product format for the pediatric form of the drug. Mr. Hurst explains that Almac worked collaboratively with the client to form a deep understanding of both the product and the patient/care-giver needs and identified mini-tablets filled into stick packs as the preferred solution. "The adult formulation was optimized to enable successful production of this multi-particulate format, and in conjunction with a number of third-party vendors, we identified, installed, and qualified bespoke equipment solutions for their specific product needs. The pediatric form of the product is now on stability with regulatory filing planned for later this year."

Ascendia Pharmaceuticals: Nanoparticles Stabilize & Boost Bioavavailability

Clients expect CDMOs to contribute more knowledge in early development, and generate quality data in pre-formulation and formulation of compounds/biologics with challenging properties that enable successful testing of new compounds in animals for pharmacology, DMPK, and toxicity studies. With regard to the latter, Ascendia Pharmaceuticals Inc. was recently presented with a preclinical compound that was ready for an animal tox study. The compound was not soluble and in a metastable amorphous form. Ascendia Founder Jim Huang, PhD, explains that it was desired to formulate the compound into amorphous nanoparticles to boost bioavailability while stabilizing the amorphous nanoparticles in aqueous phase. "Ascendia was able to use nanomilling using conditions that reduced the amorphous API to a nano-size level using a scalable wet bead milling process that enables long-term tox studies," he says.

Ascendia's technologies have been used in different routes of administration, new drug development, and life cycle management to boost bioavailability of BCS II/IV compounds, to enable long action injectables, and to produce lipid nanoparticles for encapsulation of biologicals such as protein and RNA.

"Bringing new therapeutic agents to the clinic with speed, quality, and in a cost-effective manor is a main focus for the industry and Ascendia," says Dr. Huang. "With supply chain issues, increased labor and material costs, and uncertainty in the IPO market, it becomes more important for biotech companies to successfully bring more limited molecules into human testing with quality, speed, and within a budget."

August Bioservices: Building Stronger Relationships with Innovators

As pharma and biotech companies look to partner in the earlier phases of the drug development process, August Bioservices's has structured its

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

operations to be a full-service, end-to-end provider, assisting and guiding clients all along the drug development pathway from preclinical to clinical to commercial. "Early engagement with a qualified CDMO partner mitigates risk, saves time and money for several reasons," says Ryan Downey, Director of Customer Operations, August Bioservices. "When clients find that we have the specific subject matter expertise and deep experience with similar molecules, it affords a running start and minimizes the learning curve. Also, the experience of working together through preclinical and clinical phases strengthens the understanding and characterization of the molecule and fosters strong relationships between the scientific and operational teams of both innovator and CDMO. Finally, when working with a CDMO like August that offers both formulation development and cGMP manufacturing on the same site, there is no need to spend precious resources (time, money, talent) looking for a commercialization partner."

August has also recently renovated and expanded to double its capacity. This, says Mr. Downey, puts the company in a position to service more drug sponsors during a time when finding a CDMO to take on new projects can prove difficult.

Catalent: A Multi-Layered Approach to Minimizing Supply Risks

An increasing number of smaller and virtual innovators in the development pipeline are seeking to retain project ownership for longer, and sometimes beyond commercialization. This means that support from outsourcing partners is critical to meet funding and regulatory milestones, while accelerating towards scale-up manufacturing for launch, asserts Elliott Berger, Chief Marketing Officer, Catalent. Development pipelines are healthy, but treatments are diverse, more frequently challenging, and often targeted to smaller patient populations.

"New modalities make up an expanding part of the pipeline, and these have complex development, process, and manufacturing requirements," he says. "This leads to higher investment and capability requirements, and companies will need to strategically develop or partner with organizations that have the capabilities required to bring these treatments to scale, as well as hiring, training and retaining the appropriate talent, and partnering across suppliers, regulators and other experts in order to be successful."

Innovators are increasingly looking to partners to gain expertise and guidance throughout development, selection of delivery technologies, and process and analytical development, with an eye toward scalable manufacturing and supply considerations that will save time and money up to, and beyond, commercialization. The choice of partner is important as the earlier a development partner gets involved in a program, the more it can help guide the technology choice and develop the correct scalable manufacturing methods.

Sponsors should select a partner with a demonstrated track record of success based upon the needs of the drug program, says Mr. Berger. They should also look for evidence that a CDMO closely monitors and reports supplier delivery schedules, and if it communicates effectively with key suppliers and with suppliers' suppliers, too. Assurance should be given that its supplier compliance and integrity is assessed to relevant standards.

For example, Catalent uses sev-

Flexible filling line at Catalent's facility in Bloomington, Indiana.

eral supplier monitoring tools that range from supplier performance management, third-party risk monitoring, supplier audits and critical material risk assessments, and tracking," says Mr. Berger. "These create a multi-layered approach so that Catalent can demonstrate macro and micro level risks to supply."

He shares an example of how Catalent help to minimize risk for one of its customers. "This client's drug molecule was demonstrating no exposure in humans. A day of analysis showed that while the formulation was suitable, the compound was being completely degraded after absorption in the liver. A modeling exercise could have been performed months or even years earlier saving a lot of time and money by highlighting its unsuitability as a drug. Terminating a drug candidate program can be daunting, but early outside assistance can enable sponsor companies to minimize many risks."

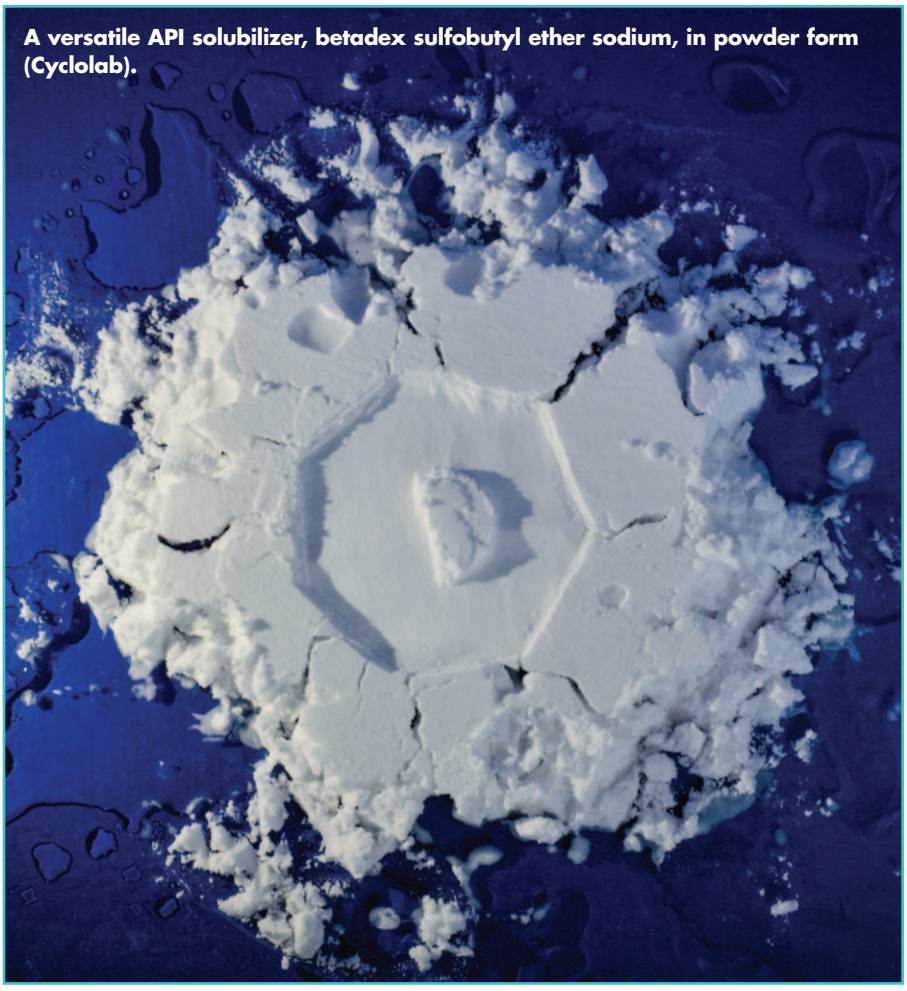
CMC Pharmaceuticals: Conducts Rigorous Studies in Early Drug Development

Developing a robust formulation, analytical methodology, and process can take significant time, resources, and funding, but leads to a reliable, reproducible process. And, understanding critical quality attributes and critical process parameters by executing scientifically rigorous studies in the early stages of drug development is necessary for a robust formulation, method, and process.


CMC Pharma provides lab services for drug product development programs, from early stages through FDA approval and commercial launch.

"Not only is this information required for FDA approval, but will result in fewer failed batches, deviations, and out-of-specification results when manufacturing pharmaceutical products, says Mike Radomsky, President & Co-founder of CMC Pharmaceuticals. "Those seeking shortcuts by skipping or eliminating these development studies may pay the price later. Dedicating scientific bandwidth, expertise, and budget to these tasks will overcome the significant formulation, manufacturing, analytical, and quality risks and will save time and money by addressing the development activities early in a product's life cycle."

One client presented a formulation issue to CMC. The drug product had a stability profile that had a very short shelf life insufficient to support even early clinical studies. "We utilized the scientific literature, pre-formulation studies, regulatory precedent, and a deep understanding of the degradation mechanism to identify stabilizing strategies," Mr. Radomsky explains. "We identified promising prototype formulations and executed studies that showed more than an order of magnitude increase in shelf life that now supports their late-stage clinical studies and commercial use."



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Cyclolab: Utilizing the Solubilization Property of Cyclodextrins

Aqueous solubilization of small-molecule APIs, including oligopeptides, in order to enhance oral bioavailability and enable preparation of injectable formulations and patient-friendly ophthalmic and nasal products, is the goal of Cyclolab. It achieves this by utilizing the solubilization property of cyclodextrins.

Dr. István Puskás, Formulation Scientist at Cyclolab, explains how the company was challenged to prepare an aqueous solution of a surfactant type of API. The API had a strong tendency to form micelles and aggregates, however, the client wanted to avoid self-assembly to enable sterile filtration of the substance and subsequent processing into the final dosage form.

"We screened suitable, pharmaceutically acceptable cyclodextrins based on their solubilization property," he describes. "After selection of the best performing cyclodextrin, the ideal pH, processing parameters, and API/cyclodextrin ratio were sought. Because the API was a weak base type compound, we found betadex sulfobutyl ether sodium (Dexolve®) as the ideal cyclodextrin for the preparation of the pre-formulation. The final result was a transparent, stabile solution of acceptable osmolality characterized in a composition well below the safety threshold of cyclodextrin exposure to patients. The resulting pre-formulation exactly matched the requirements of the customer. The elaborated process was found novel and non-obvious, therefore the customer successfully obtained a granted patent for the process based on our proposed cyclodextrin technology."

Emergent CDMO provides in-house, small- to pilot-scale lyophilization formulation development services for biologic drug products.

Emergent CDMO: Small-Scale Lyo & Nanoparticle Formulation

As product pipelines for novel biologics-based therapeutics and vaccines continue to grow and biopharma looks to outsource formulation development and manufacturing, supply chain and capacity have been a challenge industry wide. Biopharma innovators who partner with CDMOs for their novel biologic platforms are looking for the right fit for their product – the relevant expertise, experience, capabilities, and capacity in place to support the formulation development, technology transfer, and manufacturing needs of diverse molecules.

Emergent CDMO recently completed several expansions and investments to provide additional capacity and capabilities for both biologics development and drug product manufacturing to address novel therapeutic needs. For example, in development services, Tara Lorenz, Director, Commercial Development, Emergent CDMO, explains that the company has added several new high-throughput instruments for robust development and optimization for drug substance and drug product development 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 small- and pilot-scale lyophilizers and nanoparticle formulation and process development equipment have allowed us to meet industry-wide demand for lyophilized and nanoparticle products, such as lipid nanoparticle (LNP) formulations for mRNA products."

Recently, Emergent solved a client's formulation development and manufacturing issue related to a lyophilized product that did not form a cake and, therefore, powder escape was occurring during lyophilization. This suboptimal formulation was not viable for commercial production as it introduced facility and product risks, including lyophilizer cleaning, content uniformity, and container closure integrity testing.

"As a solution, our development team added one of the excipients from the reconstitution solution to the pre-lyophilization formulation blend to support cake formation," she says. "After successfully demonstrating comparability of this modified lyophilization formulation, the team developed a formulation and lyophilization process and completed tech transfer for GMP production."

Enteris BioPharma: Filling a Gap in Manufacturing HPAPI Solid Oral Drugs

Highly potent active pharmaceutical ingredients (HPAPI) are one of the most rapidly growing segments of the drug development industry and make up a sizeable portion of the pharmaceutical product pipeline due to their effectiveness. Many smaller and emerging pharma companies are now interested in developing HPAPI drug products. Highly potent API drug product handling requires specialized skill and knowledge. With the pandemic disrupting the pharmaceutical supply chain and causing material shortages, drug makers must re-think both the technical and soft skills that an outsourcing partner brings to the table during times of unpredictability.

"For companies that might need limited-sized batches and rapid turnaround, a larger CMO might not be able to meet their needs," says Angelo P. Consalvo Director of Manufacturing at Enteris BioPharma. "A niche CDMO that has the knowledge, flexibility, experience, and expertise to handle projects that may not fit with the traditional manufacturing structure would be the preferred partner of choice."

In terms of the technical skills, the

ability to achieve content uniformity and bioavailability for low-dose products are of paramount importance when working with limited quantity APIs.

Additionally, quality control, quality assurance, and containment strategies are all major factors that need to be considered when it comes to handling highly potent APIs as there is not official guidance that governs HPAPI manufacturing. Enteris BioPharma has completed the renovation of a state-of-the-art facility in northern New Jersey comprised of a team of subject matter experts with robust institutional experience, project management, and rapid problem-solving expertise, says Mr. Consalvo. "This facility utilizes a comprehensive containment strategy that consists of personal protective equipment, manufacturing containment equipment, engineering controls, facilities design, and decontamination, which prioritize worker and environmental safety."

Enteris now has the capacity and flexibility to the ensure the development, manufacture, testing, and release of Phase I to Phase III solid oral dosage clinical trial supplies, as well as small-scale commercial production. "Enteris is filling a niche that is underserved by allowing contract manufacturing for small-batch, HPAPI products."

The ability of a manufacturing partner to develop phase-appropriate manufacturing scales that will reflect both current needs and future growth is crucial to prevent additional costs. Scaling issues can lead to manufacturing re-validation and related regulatory changes, thereby delaying the programs into clinic and market, while also adding costs. Choosing a CDMO that can provide development services throughout the entire life cycle of your drug, without the need for tech transfers, can save significant time and resources. "Some companies cannot afford to wait several months or longer, whether that is for their own customers' needs or for getting a product through clinical trials," says Mr. Consalvo.

Eurofins BioPharma: Helping to Target the Undruggable Targets

Eurofins BioPharma Product Testing works with many clients in pre-clinical development, due in part to its understanding of the testing requirements for biologic and mRNA drug products. "The evolution of the biotechnology industry has led to the targeting of once undruggable targets," says Joe Page, PhD, President of Eurofins Advantar Laboratories, one of Eurofins BioPpharma Product Testing's Laboratories in San Diego. "Simply put, we have the expertise to support clients through this complex phase of development whereas some bio/pharma companies, especially smaller ones, do not have the in-house expertise to fully support this stage of development. For example, we perform cell-based potency assays."

Many early-phase drugs in development seek to edit, silence or shut down production of proteins at the DNA or mRNA level, says Dr. Page. For example, many companies are pursuing Duchenne Muscular Dystrophy treatments using gene therapy, RNA editing or gene silencing to address issues with the dystrophin protein that is needed for normal muscle function. Protein downregulation with antisense, siRNA or microRNA often employs 20 to 30 bases of DNA or RNA with a phosphorothioate backbone. These synthetic oligonucleotides are expensive to make, so conserving the amount used during clinical development is an important consideration. The use of AAV and lentivirus delivery systems, complex synthetic drugs, and high-value antibody conjugates all require the conservation of these high-value materials.

To meet this market demand, Eurofins BioPharma Product Testing has installed and qualified a gloveless, robotic, isolator filling station, the Cytiva (formerly Vanrx) Microcell. This filler is intended for filling sterile GMP supplies for clinical trials. "This system offers the lowest material line loss and the lowest amount of human interaction," Dr. Page says. "The isolator system is the industry standard for the lowest levels of extraneous particulate matter, and, with its peroxide decontamination cycle, offers the highest assurance for a sterile fill."

Other advantages of this system, he adds, include the use of nested vial-and-cap sets that significantly reduce the rejection of vials due to scratches and other defects. The nested caps eliminate operator error from the capping process. The system also uses a 100% disposable fill line and fill needle, so changeover between lots of different products can occur within a day.

In addition to offering material-saving clinical fills, Eurofins BioPharma Product Testing supports clients with pre-formulation and for-

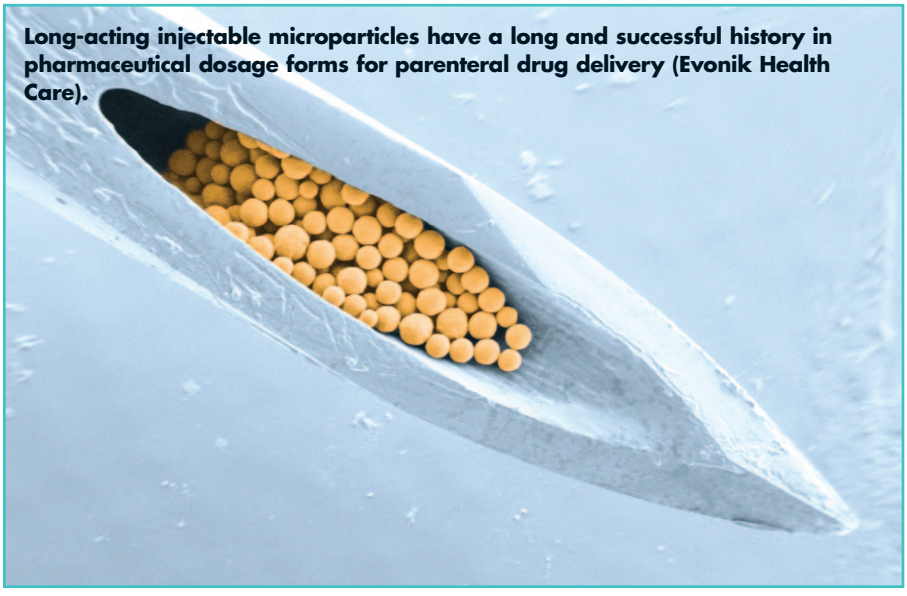
mulation services for high-value products. For example, in a recent pre-formulation study for a client, Eurofins identified a pH drift in the initial formulation prior to any lots being filled, potentially saving the client from a failed lot had this formulation gone into clinical production, explains Dr. Page. Another client was having solubility issues with an oral small-molecule formulation. "We were able to work with this client and add PEG and Tween to keep the drug in solution and potentially avert a particulate matter failure during their clinical trial. Our formulation and manufacturing activities are supported by experienced analytical scientists using state-of-the-art instruments and methods for these biotechnology products."

Evonik Health Care: Parenteral Formulation Using Polymeric Nanoparticles

A new era of medicine – that of mRNA technology – has been ushered in as a result of the COVID-19 pandemic. Evonik recognized the potential of gene-based therapeutic approaches early on and has made a targeted investment with the acquisition of Vancouver-based Transferra Nanosciences in 2016. This opened doors to working on parenteral drug formulation development using lipid nanoparticles (LNPs) and liposomes. Evonik is currently collaborating with Stanford University on a polymer-based drug delivery platform for mRNA and other nucleic acids that complement its existing LNP portfolio.

In addition, Dr. Tom Tice, Senior Director Global Technical Marketing, Evonik Health Care, explains that Evonik's microencapsulation technology for bioresorbable lactide/glycolide polymers has been translated into bioabsorbable nanoparticle technology in response to the need for cancer immunotherapy. In addition to formulation optimization, this translation also involves development of continuous particle manufacturing technologies for polymeric nanoparticles. A client came to Evonik after performing initial drug delivery formulation work for a long-acting, injectable microparticle product based on lactide/glycolide polymers.

"Using our drug delivery technologies and product development know-how, we improved formulation performance by fine tuning the polymer excipient properties and converting the solvent-evaporation batch process to an emulsion-based, continuous microencapsulation process," explains Dr. Tice. "In doing so, we provided better drug release characteristics with controlled Cmax. Also, we improved the encapsulation efficiency, achieved better injectability with smaller needles, and reduced the residual solvent. After these efforts, the formulation was ready for scale up and production of microparticle product for toxicology and stability studies and clinical trial material."



Long-acting injectable microparticles have a long and successful history in pharmaceutical dosage forms for parenteral drug delivery (Evonik Health Care).

Metrics Contract Services: Flexible Early-Phase Development

Certain segments of the supply chain, both raw material/component and process equipment/parts continue to be challenging in terms of lead times. Metrics Contract Services has reacted to these challenges by forging strong relationships with its suppliers and stocking critical spares, change parts, and raw materials for its equipment and clients, respectively. For certain dosage forms, the need to plan ahead and provide flexibility in terms of clinical dosing strategy will be important. "For example, if a clinic wants to dose in a colored opaque capsule, consider a white opaque capsule, as many CDMOs will stock that color in a variety of sizes," advises Brad Gold, PhD, Vice President of Pharmaceutical Development, Metrics

Contract Services. "Also make sure that you really need an HPMC capsule. HMPC capsules provide a good option for encapsulating APIs that have reactive moieties such as aldehydes, which may be susceptible to condensation with the gelatin peptide's reactive sites. However, consider the fact that lead times for gelatin capsules are less than half of what HPMC capsules are. So, maintaining flexibility in early-phase development with respect to compendial requirements is important."

Metrics offers early-phase formulation development, late-stage clinical trial material manufacturing, and commercial manufacturing on a single campus. During formulation development and process optimization, some of Metrics' raw materials and process equipment suppliers offer application lab services that provide data around excipient use ranges and any effect upon processing, within a specific unit operation. In the case of equipment suppliers, some are able to work with placebo blends to test out process equipment capability. "These opportunities enhance our flexibility and speed during the development and scale-up process," says Dr. Gold.

Additionally, containment option testing, verification, and qualification are important aspects in drug product manufacture, and conducting design and testing on the sponsor's site helps shorten timelines. As an example, one client came to Metrics needing to convert a drug-in-capsule to a formulated capsule for a Phase IIa clinical study. The drug was highly potent and moisture sensitive, requiring %RH of less than 30% at all times during handling and manufacture. Given the high potent banding, development and manufacture had to occur behind hard-wall isolation. Use of HEPA-filtered inlet and outlet air would be required. The idea of combining clean/dry compressed air, with ultra-low moisture contribution as 'make-up' for some inlet air, was presented and engineered as a solution. Metrics demonstrated through several dry runs that this approach was a good solution to controlling humidity levels inside a containment isolator. Formulation prototypes and clinical trial material were manufactured successfully, with state-of-the-art control for operator exposure, explains Dr. Gold. Moreover, the critical quality attribute of humidity level during manufacturing was addressed, as Metrics was able to effectively operate its high-potent containment isolators with acceptable differential pressure, while at the same time, controlling %RH to under 30%.

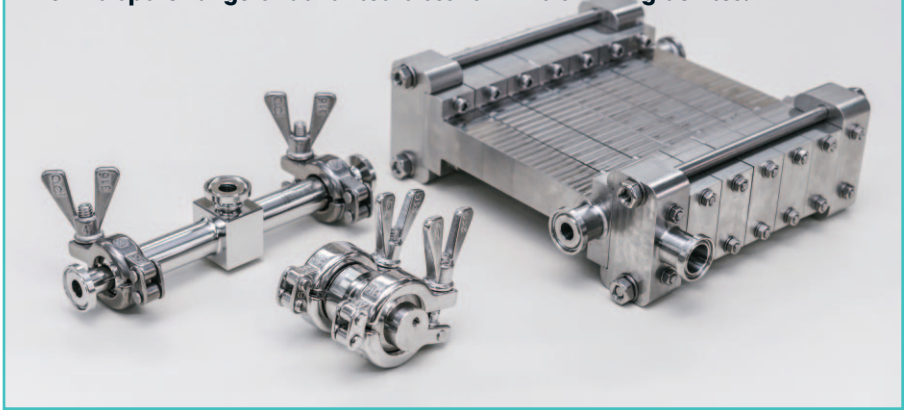
Micropore Technologies: Holistic Approach to LNP Manufacturing

At the LNP Formulation & Process Development summit this past April, a delegate observed that LNPs are probably the most complicated drug product that humans have ever tried to manufacture. A holistic approach is essential in LNP manufacturing, says Denis Smit, Commercial Director, Micropore Technologies.

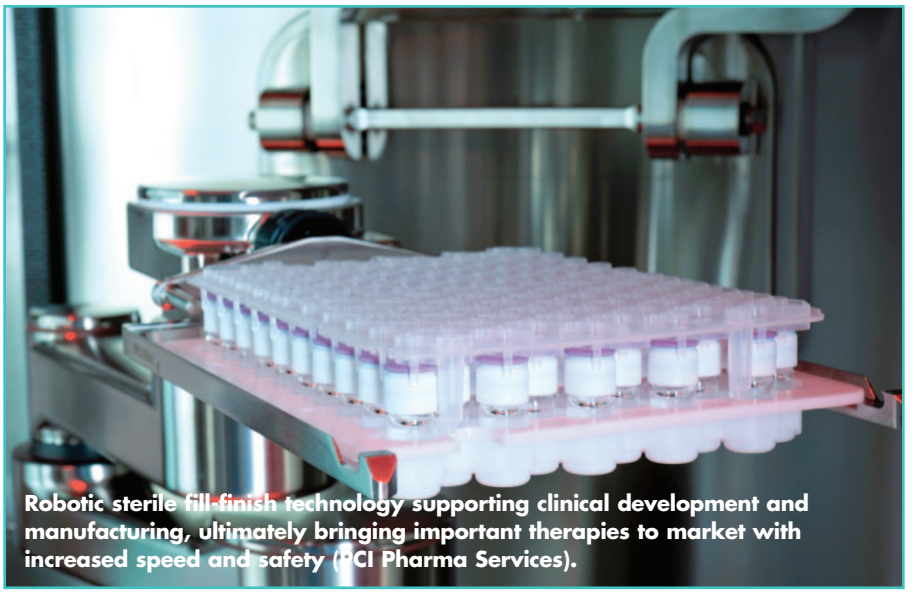
Micropore Technologies first commercialized its continuous manufacturing-scale crossflow mixing technology in 2019. Born out of more than a decade of experience in aseptic processing of microspheres, in late 2021, Micropore introduced a single device specifically engineered for early-stage discovery through to clinical trials – the AXF-mini. This device enabled the production of LNP products within a targeted particle size distribution and from which a manufacturing scale skid can be designed and built. Micropore's second-generation robust scale-up approach enables the same conditions (low pressure and low shear), the same physical mechanisms (driven by a constant and low Reynolds number), and the same geometry to be kept all the way through the process drug of development to manufacturing, explains Mr. Smit.

"The development of LNP technology to the point where it is a recognized method of delivering many different oligonucleotide payloads has

The Micropore range of advanced crossflow micro-mixing devices.



further spurred Micropore Technologies to develop further products that speed up the LNP formulation process and a new AXF-DoE device is expected to be released in the second half of 2022," he says, adding that this will meet the brief of being able to generate 300-500 microliter samples while being scalable to 20L/hr. and beyond.



Robotic sterile fill-finish technology supporting clinical development and manufacturing, ultimately bringing important therapies to market with increased speed and safety (PCI Pharma Services).

PCI Pharma Services: Fast-Tracking Drug Processing From Development to Commercialization

As an end-to-end solution provider, PCI Pharma Services continues to invest in state-of-the-art technologies to meet the needs of clients and the global marketplace. The areas in which PCI is currently investing include:

- Lyophilization and Sterile Manufacturing — At the end of 2021, PCI acquired Lyophilization Services of New England, Inc., expanding its breadth of services and building on its knowledge in specialty manufacturing and packaging at both clinical and commercial scale. To further develop PCI's sterile fill-finish capabilities, significant investments are taking place including the addition of automated sterile fill-finish technologies at its San Diego and Melbourne facilities. These robotic platforms are able to fill different sterile medications into multi-format dosage forms, including vials, cartridges, and prefilled syringes. PCI also recently announced a major expansion of capabilities and capacity in aseptic liquid fill-finish and sterile lyophilization technology, with a planned investment of $100 million at its Bedford, NH, campus, to address demand for integrated large- and small-molecule drug product solutions at clinical and commercial scales.

- Contained Highly Potent Drug Product Processing – Approximately $25 million is being invested in PCI's high-potent manufacturing facility in Tredegar, UK. This will extend the company's contained manufacturing facility and double its large-scale commercial manufacturing capacity. And a new high-potent packaging facility adds extensive packaging capacity at both clinical and commercial scales. One customer presented with a breakthrough oncology therapy needed to rapidly progress development and bypass the traditional drug development hurdles to get its innovative small-molecule drug product to patients as quickly as possible. "Utilizing our Speed to Study™ solution to streamline and accelerate early-phase development, the client leveraged our expertise in high-potent drug product processing combined with direct drug-in-capsule microdosing technology, Xcelodose®, to fast-track the molecule to commercialization, including commercial supply," explains Jeff Clement, Executive Director, CDMO Business Development North America, PCI. "This saved between one and two years of traditional CMC development while providing maximum flexibility and ultimately time and cost efficiencies."

- Greater Capacity and Biologic Packaging – Complementing its US Biotech Center of Excellence, PCI will invest $13.5 million in state-of-the-art packaging technologies at its European Commercial Packaging facility, enhancing its capacity to process the novel drug delivery systems required for biologic products, providing an end-to-end packaging solution.

Quotient Sciences: Clinical Testing & Development Under One Roof

A recent formulation development challenge that Quotient faced involved a BCS class IV candidate destined for solid oral delivery. The molecule exhibited poor solubility and permeability, with erratic absorption as an inevitable consequence. Although numerous solubility enhancement techniques exist, a critical factor in development was to ensure that the dosage form selected must be consistent and scalable to a sufficient size to support a commercial campaign. Hot melt extrusion offered not only a vehicle for manipulating the absorption properties by allowing for the incorporation of enhancement aids, but was easily controlled and scaled-up, with the additional benefit of optional continuous manufacturing. A Design of Experiment approach was successfully used to select a polymer matrix that would provide the dissolution profile required by the customer. Despite some stability challenges that presented themselves in early prototypes, a well-performing formulation was selected for Phase I studies, says Helen Baker, Director, Pharmaceutical Sciences, Quotient Sciences.

Quotient has its own Phase I clinical pharmacology units that are fully integrated with its drug substance and drug product facilities. "Offering both clinical testing and drug development capabilities under a single organization enables customers to experience a drastically reduced time investment for the development of products, rapid delivery and interpretation of clinical data, and subsequent reformulation that comes from each team being fully aligned," says Ms. Baker.

Quotient Sciences also offers HPAPI handling capabilities in both its US and UK drug substance and drug product facilities in response to a rising demand in the high-potency pharmaceutical ingredient (HPAPI) space. "Clients are increasingly seeking out CDMOs capable of rising to the challenges that processing those compounds presents," she says.

Thermo Fisher Scientific: New Sites Dedicated to Cell Therapy & Plasmid Manufacturing

Digitalization, big data, and artificial intelligence will accelerate the transformation of the pharmaceutical industry and enable companies to improve drug development and patient care beyond the treatment of diseases. Digital solutions enable the shift from a disease focus to an integrated approach from prevention, screening, diagnostic, treatment, and aftercare. Novel associations between the human microbiome, health, and disease are constantly emerging, leading to new diagnostics and therapeutics, enhancing personalized medicine.

"Precision medicine, cell and gene therapy, and immune-oncology are fueling new ways of prevention and detection with the potential to revolutionize the treatment of many diseases," says Anil Kane, PhD, Senior Director, Global Technical Scientific Affairs, Pharma Services, Thermo Fisher Scientific.

Thermo Fisher Scientific, for instance, has integrated its capabilities across the operational value chain to enable the development and commercialization of mRNA therapeutics. "We have over a decade of experience in cGMP manufacturing of raw materials and 20-plus years of experience in complex sterile manufacturing," Dr. Kane says. "Our global network of sites with mRNA capabilities includes cGMP manufacture, formulation with liquid nanoparticle (LNP), sterile fill and finish, and logistics and supply chain networks."

This year, Thermo Fisher will open a 300,000-sq. ft. viral vector manufacturing facility in Plainville, MA, a new cell therapy development and cGMP manufacturing center at the University of California San Francisco, Mission Bay campus, and a new cGMP plasmid manufacturing facility in Carlsbad, CA. ◆

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PLATFORM TECHNOLOGY

Confident Silence: Delivering on the Promise of siRNA Therapies

By: Giles Campion, MD

INTRODUCTION

Thirty years ago, I moved from medical practice in rheumatology to industry because I wanted to help develop targeted medicines that would treat patients more effectively and safely than the available options. The same aim, amplified by the potential of targeted therapies based on gene silencing (antisense), motivated my move to Silence Therapeutics, which is developing siRNA therapies for many diseases.

The great promise of siRNA is its ability to hit "undruggable" targets – those not amenable to small molecules or biologics. siRNA are targeted medicines that are also precision medicines, because they engage and silence their mRNA targets via the precise mechanism of Watson-Crick base pairing.

Additionally, conjugation of siRNAs to the amino-sugar molecule GalNAc enables highly specific delivery of siRNAs to the liver, which expresses thousands of genes. This exquisite targeting mechanism, elucidated within the past decade, coupled with the precision of siRNA molecules themselves, has opened the door to a whole new arena of targeted therapies, with the first siRNA product receiving regulatory approval in 2018 and two others following suit since then.

As a physician, I find siRNA technology exciting for its potential to create therapies for many diseases, especially rare diseases, which lack effective treatments. As a drug developer, I find it appealing because it provides me with added confidence, well before a product enters clinical testing, which is uncommon for other therapeutic modalities.

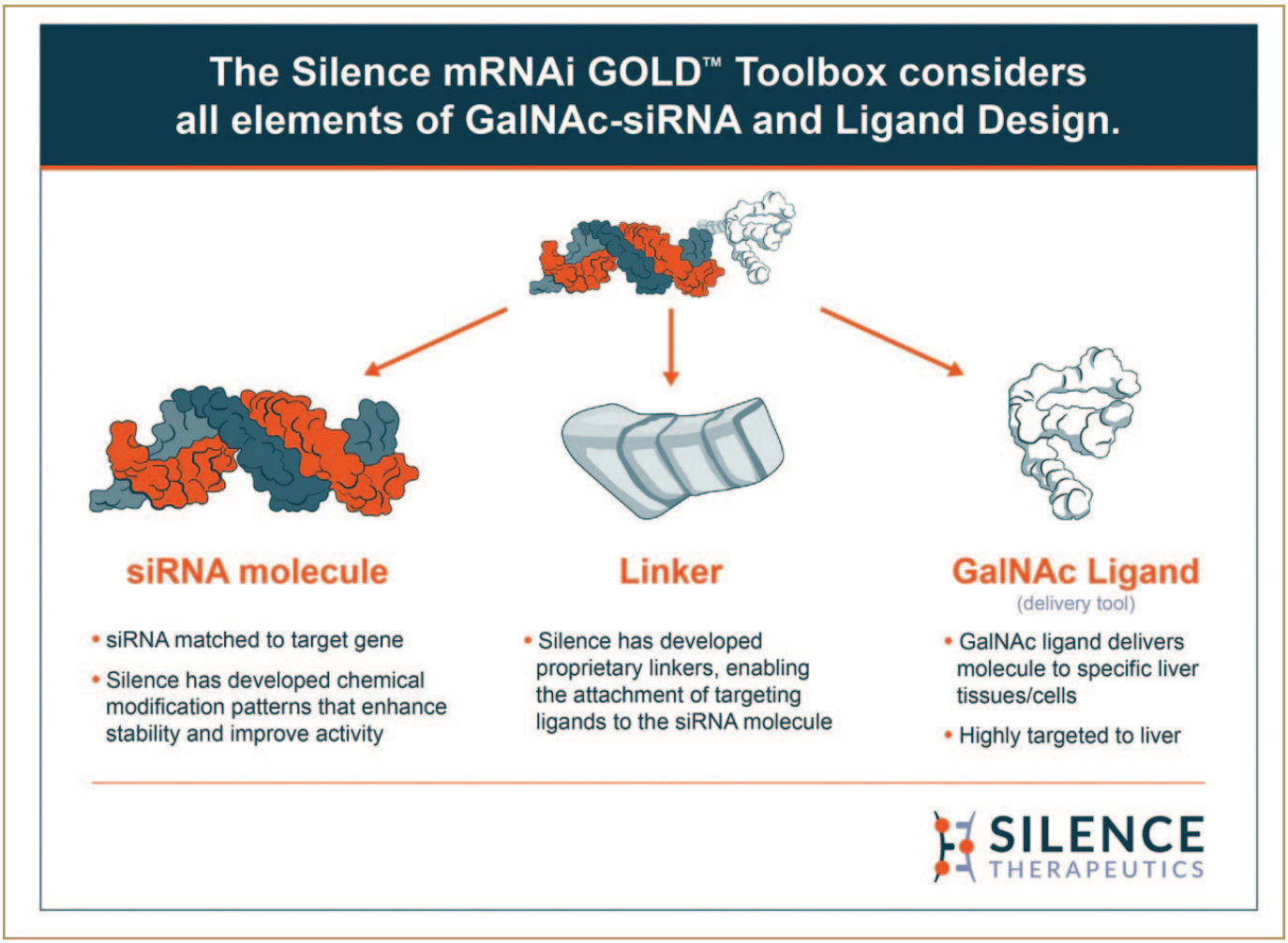
THE CAUSES FOR CONFIDENCE

The selection of diseases and gene targets for siRNA therapies can appear daunting because of the myriad possibilities: of the approximately 30,000 genes in the human genome, the liver expresses about 14,000, and only 1% of those are targeted by publicly disclosed siRNAs. This leaves a vast "white space" of potential targets and therapeutic opportunities. When stepping into this space, Silence applies two key criteria to select diseases and targets for our mRNAi GOLD™ platform.

The first criterion is unmet need, which is key to me as a physician. I want to pursue diseases in which patients lack suitable options and develop precision medicines that offer those patients hope and a better, longer life.

The second criterion is a clear "line of sight" from the proposed genetic target to the disease involving that gene. This clarity is possible with siRNA technology because it targets a key enabler of the gene – its mRNA – leading to downstream silencing of encoded protein. By selecting a gene critical to the disease process, we can therefore have confidence that silencing the gene's mRNA will affect disease progression.

Target selection today is aided by human genetic databases, such as the UK Biobank, that allow us to link a gene to its biological processes and characteristics in humans (phenotypes). We mine these databases to understand whether interfering with a certain gene could treat a disease; and, if so, if other systems might be affected as unwanted side effects. Our goal is to target a gene that has little or no effect on phenotypes outside the disease. In fact, we have made this whole approach to de-risking the target central to our discovery machine.



Lipoprotein(a) or Lp(a), the target of our SLN360 product candidate, is a good example of this. The only phenotype linked to silencing of the *LPA* gene that encodes the Lp(a) protein relates to the relative risk of cardiovascular disease: high levels of Lp(a) are associated with high risk; low levels are associated with low risk. Some individuals have zero levels of Lp(a) and for them, the only known phenotype is one with a much reduced incidence of cardiovascular events.

After selecting a target gene, we apply machine learning (artificial intelligence) and other *in silico* techniques to maximize the siRNA's silencing effect on the target's mRNA, while minimizing the siRNA's potential to bind other mRNAs and produce unwanted side or off-target effects. This ability to predict and screen out siRNA sequences that could cause side effects is possible due to the precise mechanism of nucleotide base pairing, and contributes to the wide safety margins we anticipate with our siRNA molecules.

Indeed, while safety is important in treating any disease, minimizing the potential for side effects is especially important in treating chronic diseases, such as hyperlipidemia, where it can take decades for patients to experience any overt symptoms from the condition. Such patients are unlikely to tolerate a therapy with even minor side effects that interfere with their quality of life.

Additional chemistry on our platform links GalNAc ligands to the siRNA to optimize its uptake by liver cells – further adding to safety by reducing or eliminating uptake by tissues not containing the targeted mRNA. This is another feature that sets siRNA therapies apart from small molecule drugs, which often act by targeting proteins and can be highly unpredictable in terms of what tissues they will enter, how they will be metabolized, and which side effects they could have.

Collectively, our developmental approach provides us with a confidence in the safety and efficacy of an siRNA therapy that isn't always possible with small molecule drugs. That confidence translates to lower clinical failure rates for siRNA therapies: current information tells us that about 50% of siRNAs that successfully complete Phase 1 will successfully complete Phase 3, compared with just 9% for small molecules.

ONE GENE, ONE FUNDAMENTAL PROCESS, MANY RARE DISEASES

In addition to enabling the development of an siRNA therapy for one specific disease, such as hyperlipidemia, understanding the relationship between a gene and its phenotypes can also reveal the possibility of developing a single siRNA product for multiple diseases, especially rare ones, in which the same fundamental biological mechanism is dysregulated.

Iron flux is a good example of a fundamental mechanism that is disrupted in a number of rare diseases. While we depend on iron, in the form of the oxygen-carrying protein hemoglobin in red blood cells, for air exchange, iron itself can be toxic. For this reason, the body has iron-regulating mechanisms that help protect our tissues against toxic iron build-up.

Hepcidin is a key regulator of iron: high levels of hepcidin restrict its availability, while low levels of hepcidin can allow too much of it to circulate. Hepcidin itself is negatively regulated by *TMPRSS6*, which is the gene target of SLN124: silencing this gene's corresponding mRNA increases hepcidin expression levels, resulting in lower iron levels into the blood.

The phenotype of *TMPRSS6* makes it an attractive target for siRNA. Inherited mutations in the *TMPRSS6* gene cause iron-refractory iron deficiency anemia (IRIDA), a type of anemia that does not respond to oral iron therapies; but that is the only phenotype associated with loss-of-function defects in *TMPRSS6*. This means that silencing *TMPRSS6* is not likely to have effects outside of the processes that produce hemoglobin and red blood cells. This validation in terms of human genetics increases confidence in the target both in terms of effect and safety.

In diseases like beta thalassemia and myelodysplastic syndromes (MDS), the body has disrupted the mechanisms that protect it from iron overload. Genetic mutations interfere with the bone marrow's ability to make normal red cells (erythropoiesis), leading to anemia. Although this anemia is not caused by a lack of iron, the body tries to compensate by releasing additional iron from body stores to help make more red cells. It does this by suppressing the level of the key iron regulator hepcidin. This in turn causes an excess of free iron that poisons the bone marrow and further reduces erythropoiesis, exacerbating the anemia as well as causing problems in other organs, such as the liver, endocrine system, and heart.

The dysregulation of erythropoiesis in beta thalassemia and MDS can also cause splenomegaly (enlarged spleen) for two reasons: the spleen begins to produce red blood cells to compensate for the bone marrow dysfunction; and the spleen has to work harder to remove immature, improperly formed red blood cells from circulation.

We have shown in preclinical animal models of disease that silencing *TMPRSS6* to up-regulate hepcidin improves erythropoiesis in the bone marrow, reduces iron overload and spleen size, and increases levels of hemoglobin. Targeting the iron-regulating mechanism to increase hepcidin levels and thereby decreasing iron levels, as Silence's SLN124 does, could improve erythropoiesis, sparing patients the need for multiple blood transfusions and the risk of organ damage from resulting iron overload. By contrast, iron-chelating therapies do not have all of these therapeutic benefits, because they only "skim" excess iron from the blood without modulating the underlying mechanism that results in that excess.

Polycythemia vera (PV) – our most recently announced program for SLN124 – is another disease where regulation of iron levels by hepcidin can be a therapeutic alternative. PV involves the over-production of red blood cells as a form of cancer, increasing not only red cell mass – the total amount of the cells in the body – but also the overall thickness and stickiness of the blood. This leads to a variety of adverse symptoms, as well as a fourfold higher risk of cardiovascular events, such as heart attacks and strokes.

Increasing hepcidin levels in PV restricts the amount of available iron, effectively placing the bone marrow on a "low-iron diet" that reduces red cell mass, hemoglobin levels, and hematocrit. In a murine transplant model of PV, we and our Australian collaborators have shown that silencing *TMPRSS6* reduces these blood markers and the symptoms of the disease.

There are two additional rare diseases, and a widely used treatment procedure, in which increasing hepcidin by silencing *TMPRSS6* could be therapeutically beneficial.

One is hereditary hemochromatosis, in which mutations in one of several genes cause excess iron absorption and iron overload. As in beta thalassemia and MDS, increasing hepcidin can treat the disease by reducing levels of iron and its availability.

Another is sickle cell disease (SCD). Studies in preclinical models of SCD have shown that decreasing iron levels reduces the amount of sickling (deformity) of red blood cells and the incidence of sickling-related thrombotic events.

Finally, iron regulation could be beneficial in hematopoietic stem cell transplantation, which is used to treat a range

of blood cancers and non-cancerous conditions. This procedure involves ablating the existing bone marrow to make way for the stem cell graft; this ablation shifts a huge load of dead, iron-laden blood cells into the circulation. Retrospective studies suggest the acute release of toxic iron from the ablated cells can adversely affect the survival of the stem cell graft and increase the risk of potentially lethal infections in patients. If levels of the iron could be reduced by up-regulating hepcidin, we believe we could improve survival and engraftment outcomes in hematopoietic stem cell transplant patients.

What I find fascinating and exciting here is that one siRNA therapy has the potential to treat at least five rare diseases and improve outcomes in transplantation procedures to treat many other diseases – all by precisely targeting a single gene regulating a single fundamental process in the liver.

THE NEXT FRONTIERS IN SIRNA

While the liver offers plenty of fertile ground for developing siRNAs therapies to treat many diseases, many disease-related genes are not highly expressed in the liver. For this reason, the next great challenge in the field is delivering siRNA to tissues outside the liver. Finding another targeting ligand with the exquisite specificity of GalNAc for a tissue outside the liver is the "Holy Grail" and likely to be challenging. Meanwhile, researchers and companies are experimenting with various delivery methods: conjugating siRNAs to antibodies or peptide ligands, or loading siRNA into lipid nanoparticles or exosomes.

For many years, I have been passionate about RNA technology in general and, more recently, the benefits that targeted, precision siRNA medicines can bring to patients in need. It is rewarding to see that this technology is finally coming into its own, with the promise of delivering even greater benefits in the near future. ◆

BIOGRAPHY

Dr. Giles Campion joined Silence Therapeutics as Head of R&D and Chief Medical Officer in June 2019 and was appointed as an Executive Director in May 2020. He is an expert in translational medicine and a highly experienced biotech and pharmaceutical professional across many therapeutic areas, most recently in orphan neuromuscular disorders. He has held senior global research and development roles in several large pharmaceutical, diagnostics, and biotech companies, including responsibilities at the board level. Dr. Campion previously served as group Vice President, Neuromuscular Franchise at BioMarin Pharmaceutical Inc., or BioMarin, from February 2015 to March 2016, following BioMarin's acquisition of Prosensa Holding N.V., or Prosensa. He served as Chief Medical Officer and Senior Vice President of Research and Development at Prosensa from 2009 until its acquisition by BioMarin and held executive Research and Development positions at SmithKline Beecham, Novartis and GE-HealthCare. Dr. Campion is also a co-founder of PepGen Ltd. He earned his bachelor's and doctorate degrees in Medicine from the University of Bristol and is listed on the General Medical Council (UK) Specialist Register (Rheumatology).

Drug Development
EXECUTIVE

Alessandro Maselli

President & Chief Operating Officer

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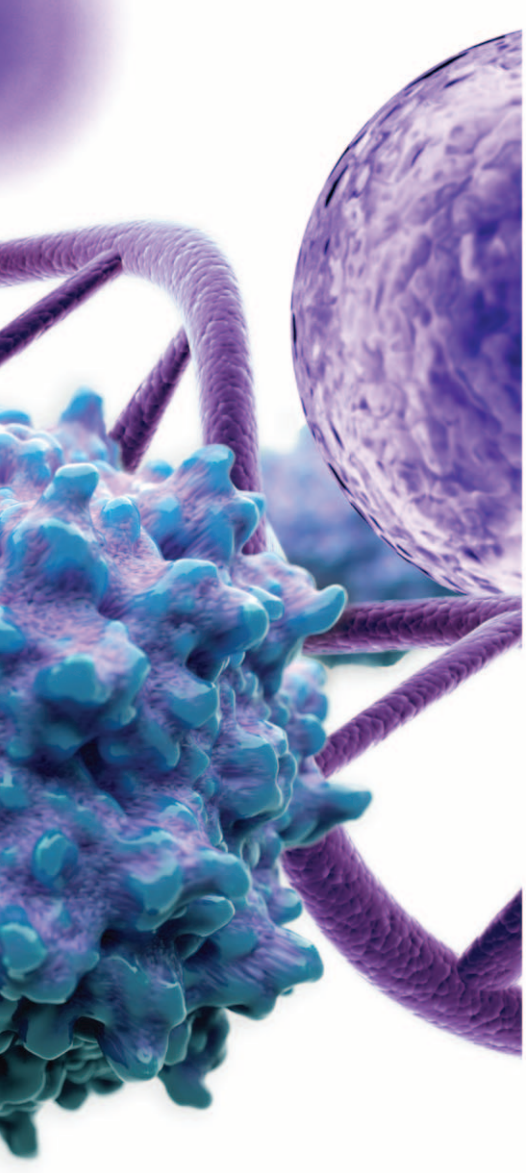
With a history going back more than 85 years, Catalent has grown from its roots in Robert Pauli Scherer's invention of the "rotary die" process for softgel encapsulation to become a leading development and manufacturing provider. Its business has now evolved to enable its partners in pharmaceutical, biotech, and consumer health to optimize product development, launch, and commercial supply of nearly 7,000 products to patients around the world. Each year, the company produces more than 70 billion doses of medicines and consumer health products for more than 1,000 customers. *Drug Development & Delivery* recently interviewed Alessandro Maselli, President and Chief Operating Officer of Catalent, about its approach to drug development partnerships as he prepares to become the company's new President and Chief Executive Officer on July 1, 2022.

Q: What are the biggest changes in terms of the industry as a whole that you have witnessed as a company throughout the past decade?

A: There are three changes I consider most significant. The biggest we've seen is the nature of our customers and their expectations of Catalent as a partner, so we've continuously evolved and adapted to meet their needs - while anticipating the future demands of the market. Whereas 10 years ago, late-stage drug development was mostly the preserve of big, multinational pharmaceutical companies that would acquire clinical programs from smaller biotech companies once proof of concept had been established, it is now far more common for smaller and virtual innovators to use development and manufacturing partners to retain project ownership for much longer, occasionally through to commercialization.



The nature of drug projects has changed too. The pipeline is large and healthy, but it is rare for any treatment to have the potential of a "blockbuster" in the way we have historically understood, and the molecules in development are more frequently challenging, diverse, and targeted. Oral dose remains the gold standard, but small molecule development is now often focused on complex drugs, many of which have poor solubility and bioavailability, so delivering them orally requires specialized experience. Biologic drugs are now well-established, but there are efficiencies still to be gained in their development and production, and the emergence of new modalities - such as mRNA drugs and cell and gene therapies - require more specialized analytical and development expertise and capabilities, and often bespoke and less efficient manufacturing solutions.

Finally, given that smaller companies have limited internal resources, and often little or no manufacturing assets, the role of a contract development and manufacturing organization (CDMO) has changed from a purely transactional partner into being a strategic development partner - offering expertise and guidance throughout the development stages toward commercialization. As a result, we work closely with our partners to understand their goals and provide frequent input and guidance on the precise development path and the manufacturing technology needed to deliver the drug to the patient. This requires mutual trust, so deep relationships with proven partners and an understanding of customers' individual needs has become more important than ever.

Q: How has Catalent evolved to meet these changing requirements?

A: We've grown significantly over the past decade, in both the number of people we employ and the areas in which we work. We have invested billions of dollars in both organic and inorganic assets, and are continually enhancing our physical sites, and the expertise that we can offer to customers, to ensure

we provide broad and deep support for a vast array of drug development projects.

The importance of our people's expertise cannot be overstated. We're extremely proud of the high-caliber talent we're able to attract and, just as important, the learning and growth opportunities we provide our people. It's no exaggeration to say that without our highly skilled, dedicated workforce, all the technology in the world still wouldn't be enough to meet our customers' needs.

Our global workforce now exceeds 19,000, including 2,500 scientists and technicians on four continents, and we launch some 150 new products every year with our customers. It is vitally important for us to share the knowledge and experience we gain as we work on these programs, so we've invested in creating tools and specialized networks, in order that our experts can learn and collaborate - regardless of where they are located. This collaboration takes many forms, from in-house learning to sharing solutions for specific circumstances, and we've been able to adopt proven techniques and practices to bring rigor to the development and manufacture of new modalities.

We've also focused on investing in the novel technologies, capabilities, and capacity necessary to maintain Catalent's leadership position. To meet the growing demand for advanced therapeutic modalities, we've broadened our scientific expertise to include biologics, antibody-drug conjugates, cell and gene therapies, and mRNA-based therapies. We actually entered the mRNA market before the explosion in interest created by some COVID-19 vaccines so we were well-positioned to serve customers working in this area. That's because we continually evaluate emerging technologies, with a view to not only how they will assist in early development, but also how the dose form could be scaled to commercial volumes. This means that, when the demand presents itself, we are able to immediately take the next steps and transform a concept into a viable prospect, which reduces the risk of unnecessary cost or waste when pursuing with difficult-to-scale or novel dose forms.

Q: From a business perspective, how did COVID affect Catalent's strategy, and how will these changes direct its business plans in the future?

A: The pandemic came at a time when Catalent was in the process of expanding capacity at several sites, which allowed us to meet an immediate demand to support more than 100 COVID-19-related vaccine and therapeutic programs. We were able to accelerate some of these expansions and make further investments, making us a strategic partner for many customers that could play a critical role in battling the pandemic.

At same time, the high utilization of these assets because of the high volumes needed for vaccines and therapies allowed us to reinvest in additional capabilities and growth opportunities beyond pandemic-related volumes.

We made investment decisions with a rigorous but nimble approach, identifying areas that could be in high demand after the pandemic, such as pre-filled syringes and for fill and finish, commercial-scale cell therapy and flexible biomanufacturing suites for viral vectors, as well as mammalian cell manufacture.

It's my belief that the main legacy of the pandemic for our industry will be CDMOs are viewed not only as essential parts of the healthcare ecosystem – which we of course are – but more as true strategic partners now, enabling companies to achieve more than previously thought possible.

Q: What is the potential of cell and gene therapies, as we seem to have accelerated very fast in this area?

A: Cell and gene therapies offer patients the prospect of longer-lasting and potentially permanent treatments for diseases that may otherwise lead to a lifetime of debilitation or early mortality. We've witnessed huge growth in research and development in this area, fueled by recent regulatory approvals and Fast Track designations.

Catalent has followed a bifurcated approach to meet customers' needs in this area. First, for gene therapy, we waited until the technology had matured and there was greater validation of the use and development of this therapeutic modality before entering the market at scale. We acquired Paragon Bioservices and its proven adeno-associated virus (AAV) technology in 2019, which allowed us to forgo any delay in building infrastructure, and gave us access to established partner programs at various developmental and clinical stages. I'm proud to note that the facility near Baltimore we acquired then was the first CDMO location approved by the FDA for production of a commercial gene therapy.

For cell-based therapies, we entered slightly earlier in the maturation cycle, as the pipeline was already well established and the infrastructure needs were not as demanding. We acquired MaSTherCell in Gosselies, Belgium, in 2020, and have subsequently built a cell therapy campus there through the acquisition of other nearby facilities and the

development of complementary services. We recently acquired a commercial-ready facility in Princeton, New Jersey, from Erytech Pharma, through which we added multiple cGMP manufacturing suites as well as laboratories for analytical, quality control, and microbiology testing.

Additionally, we saw a significant opportunity to enter and rapidly scale our capabilities in plasmid DNA manufacturing, both at clinical and commercial scale, through additional acquisitions at our Gosselies campus and organic investment at one of our Maryland facilities.

Q: How can technologies such as those mentioned in Pharma/Bioprocess 4.0 accelerate drug development?

A: Whether we call it industry, pharma, or bioprocess 4.0, "digital integration" has been referred to as the fourth industrial revolution - bringing together business processes with digital automation. Innovation can be challenging in our highly regulated environment, but, as the pandemic further emphasized, fast decision making and adaptability are critical to driving process improvement and eliminating waste. Catalent can use its size and scale to advantage, integrating not only at site level, but also across its network, and ultimately with its supply chains and customers, so they all have common data from which to make decisions. The challenge to the industry is in moving from custom integration toward a standardized approach. Our aim, and that of many of our customers and peers, is to run our business using real-time data and remove delays associated with paper-based systems. In the near future, we will add analytical tools to extrapolate data trends and artificial intelligence to optimize processes. One example of this would be using tools in biomanufacturing that continually monitor bioreactor conditions and can make automatic adjustments to optimize production yields.

Q: What do you see as the biggest disconnect /challenge in the industry at the moment, and how can a company such as Catalent look to bridge it?

A: As mentioned earlier, the role of CDMOs has changed from being contractors that customers used to "plug the gaps" in development for specific technical needs, or provide surge capacity, to partners that are a critical and strategic component in customers' plans.

New therapeutic modalities bring the great promise of treating and curing patients but, at same time, create new challenges for the industry in supplying them efficiently. Patient populations tend to be smaller, as do drug product volumes. New modalities also tend to rely on capital-intense technologies and assets and comparatively inefficient manufacturing processes. These dynamics pose significant challenges for innovators, which need to deploy capital for manufacturing assets efficiently. This is why working with the right CDMO partner has become so critical, one that can achieve the economies of scale necessary to make these treatments accessible and available to more patients, reliably and at speed.

Our ambition in the biologics and small molecules space is to be a crucial partner to maximize the chances of success, and support innovators throughout the clinical development and commercialization journey. We achieve this through the development and application of enabling technologies, such as our GPEx® Lightning technology, which significantly accelerates the development of stable cell lines and generates the highest titers of biologics, such as monoclonal antibodies. In addition, we are expanding our world-class assets across our global manufacturing network to offer our partners the capacity and capabilities to support products throughout their life cycles.

We seek to support partners of all sizes while offering all major drug development platforms. With our expertise and team of thousands of scientists around the world, we can work across and solve a full spectrum of development and delivery challenges, whether for a large pharma customer looking to build deep partnership structures to support multiple programs at various stages throughout the development and commercial route, or for a virtual company, with no physical assets and one drug candidate, looking for a partner that can add expertise and assist in development decisions and be flexible in a fast-moving process.

Although these paths can be different, we know that the end goal of all our customers is to provide patients with the very best drug treatment possible, and together, this is a goal we strive toward each day. ◆

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FERRIC OXIDE YELLOW **(Tablet/Capsule coat)**	0.32 mg
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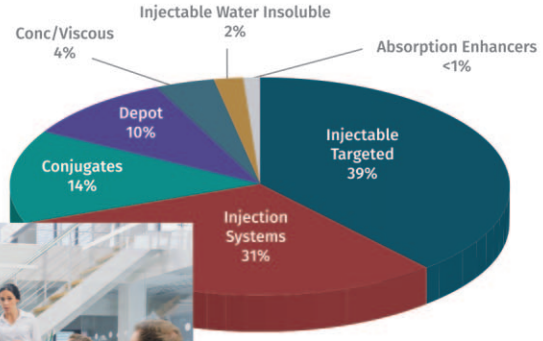
FD&C RED NO. 40 **(Tablet/Capsule coat)**	
FD&C BLUE NO. 2 **(Tablet/Capsule coat)**	

Evaluate New and Promising Technologies



Injectable Drug Delivery Technologies

Screen Potential Partnering and Investment Opportunities

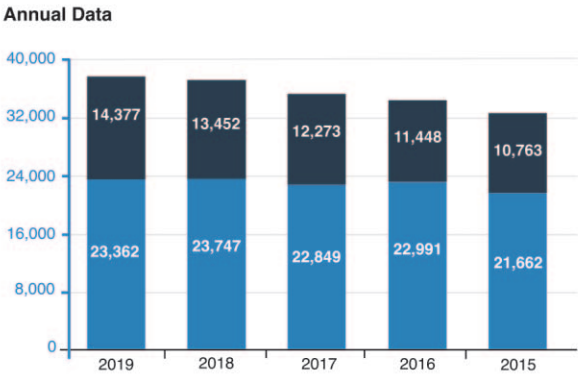
Select Companies

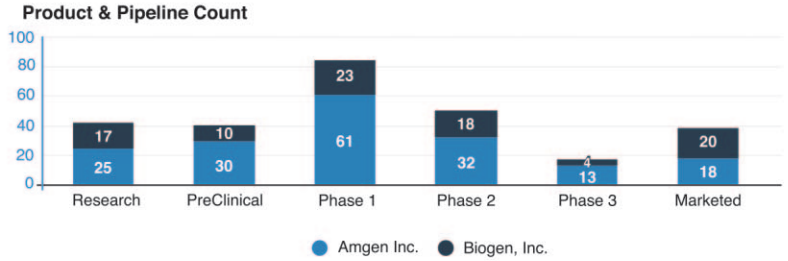
Amgen Inc. x

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





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CLINICAL TRIALS SOLUTIONS

Cracking Down on the Rising Costs of Drug Development: How Pinpointing the Complexity of Individual Patients Can Improve Success Rates

By: Dominique Demolle, PhD, and Erica Smith, PhD

DRUG DEVELOPMENT IN THE PAST 2 DECADES: AN EVOLUTION OR A REVOLUTION?

Drug development has changed significantly throughout the past 2 decades. Nearly 20 years ago, in 2004, the FDA was launching the Critical Path Initiative with the objective of more efficiently transitioning from discovery to NDA. At the same time, personalized medicine was in its infancy, and the pharma industry was already focusing their efforts on reducing the time and cost of clinical trials. The ambitions were lofty, challenging, and occasionally at odds with each other. Twenty years later, the cost of bringing a new treatment to the market has increased from $800 million to about $2.6 billion, and development timelines remain unchanged.[1] Does it mean that our industry has failed to achieve a major transformation and that this quest is hopeless? This conclusion would be too simplistic and quite frankly untrue.

In truth, we have made great leaps forward in areas from drug discovery to personalized medicine. New types of therapies ranging from small and large molecules to stem cells, drug-device combination products, gene therapies, and novel delivery technologies have emerged. Personalized medicine has moved to the forefront with more generalized use of biomarkers, surrogate markers, genomics, epigenomics, proteomics, metabolomics, and imaging. Beyond this, new trial designs have also evolved (for example, Bayesian adaptive clinical trial design). Drug development has indeed progressed substantially, and personalized medicine has made a great step forward. Innovation has addressed some of the most critical needs for treatment, as evidenced by the consistent and sustained decline in cancer death rates, and all would agree that any patient is better treated now than 20 years ago.[2]

CLINICAL TRIAL COMPLEXITY

Yet, with all this progress, we, as an industry, are still working diligently to reduce clinical development cost and timelines and to push the boundaries of treatment optimization. With new drug types and personalized medicine comes increased complexity while demonstrating optimal benefit versus risk remains a challenge. While some disease and patients have found better cures, the overall probability of technical in most therapeutic areas remains low (Figure 1).[3] The major drivers of drug development cost, timeline, and failure persist, with the inability to demonstrate adequate efficacy or safety as the largest and most difficult obstacles.[4]

Our main challenges include the following:

- High number of patients required to demonstrate efficacy, driving long recruitment timelines and high trial costs
- Increased data per trial patient (increased number of procedures or outcomes) needed to characterize patient response to treatment
- Complexity and cost of the study procedures themselves (imaging, biomarkers, etc)

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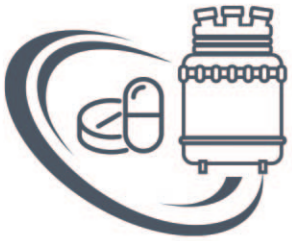

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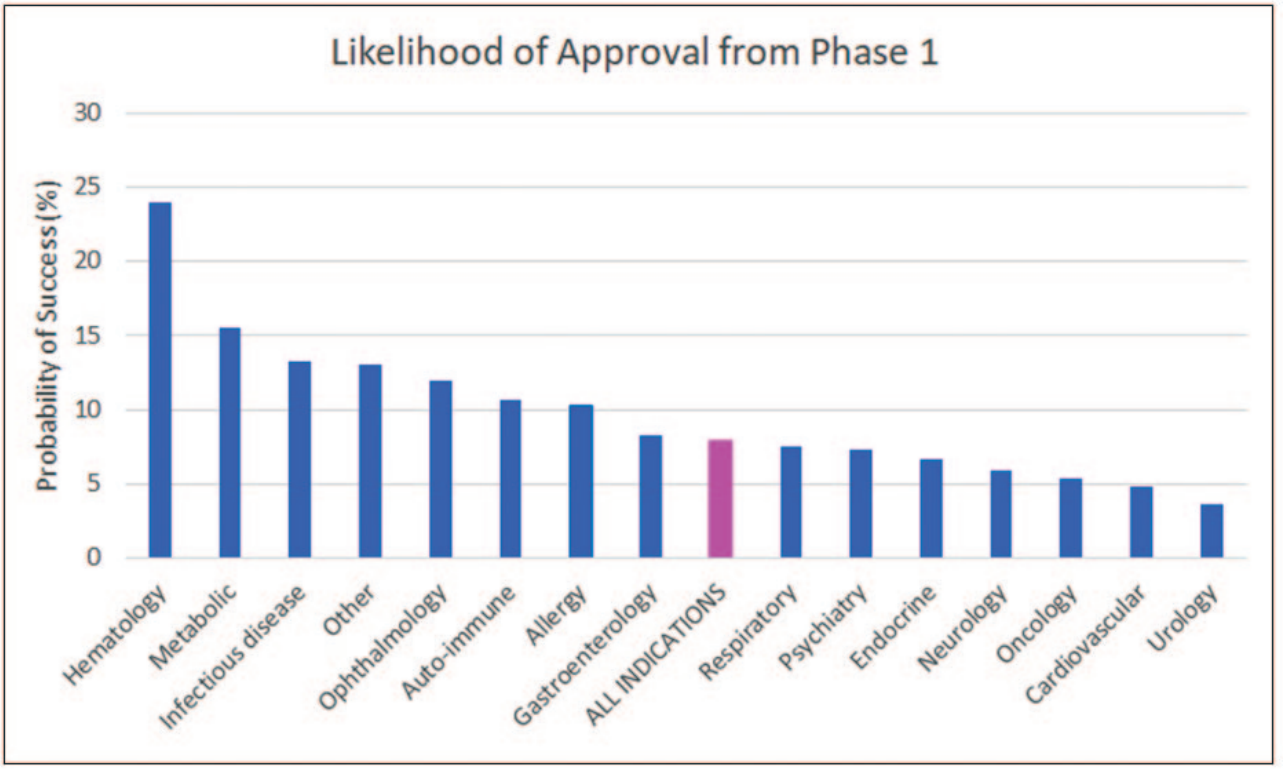
FIGURE 1



The likelihood of approval of drugs from Phase 1 across indications remains low, less than 8%, with indications like neurology and psychiatry having some of the lowest success rates. (Adapted from Clinical Development Success Rates and Contributing Factors 2011-2020)[3]

- Operational complexity to achieve trial goals [geographies, number of sites; suboptimal patient recruitment/enrollment (due to rigid inclusion criteria, drop out, non-compliance, etc)]

Considering only external costs, the median cost of a clinical trial patient varies between $10k and $30k, depending on the therapeutic area.[5] Let's explore these sources of inefficiency in more detail.

ONGOING INITIATIVES TARGETING TRIAL CONDUCT EFFICIENCY

To address these remaining obstacles, operational optimization strategies have been launched and broadly implemented for several years, including quality by design, blockchain, and process optimization with lean and six sigma approaches. With these methods, efficiency gains result from operational rationalization and improvement, as well as generating data of better quality. For example, the Clinical Trials Transformation Initiative, CCTI has made progress with Transforming Trials 2030. Among recent efforts, they are interested in facilitating the development of recommendations for the conduct of decentralized clinical trials, an essential step forward in the conduct of clinical research.

Historically, the pharmaceutical industry makes incremental improvements over time, yet the unexpected disruption caused by Covid-19 is motivating companies to make more radical transitions to reach their corporate goals. Initiatives like Modernizing Clinical Trial Conduct from Transcelerate will use data and experience issued from solutions implemented during Covid-19 and evaluate them across the board. In all cases, the industry will benefit from having all stakeholders, including regulators, simultaneously focus on the patient voice and patient-centric approaches.

COULD PATIENT-CENTRIC APPROACHES IMPROVE EFFICACY EVALUATION?

Inability to demonstrate efficacy of experimental therapeutics is a major source of late-stage clinical trial and program failure, and significant efforts have been invested in the identification of factors that can improve "assay sensitivity" in indications with high failure rates like pain and depression.[4,6] One option is to focus on data variability – or the "noise" in clinical trial data resulting in part from interpersonal differences in response to treatment.

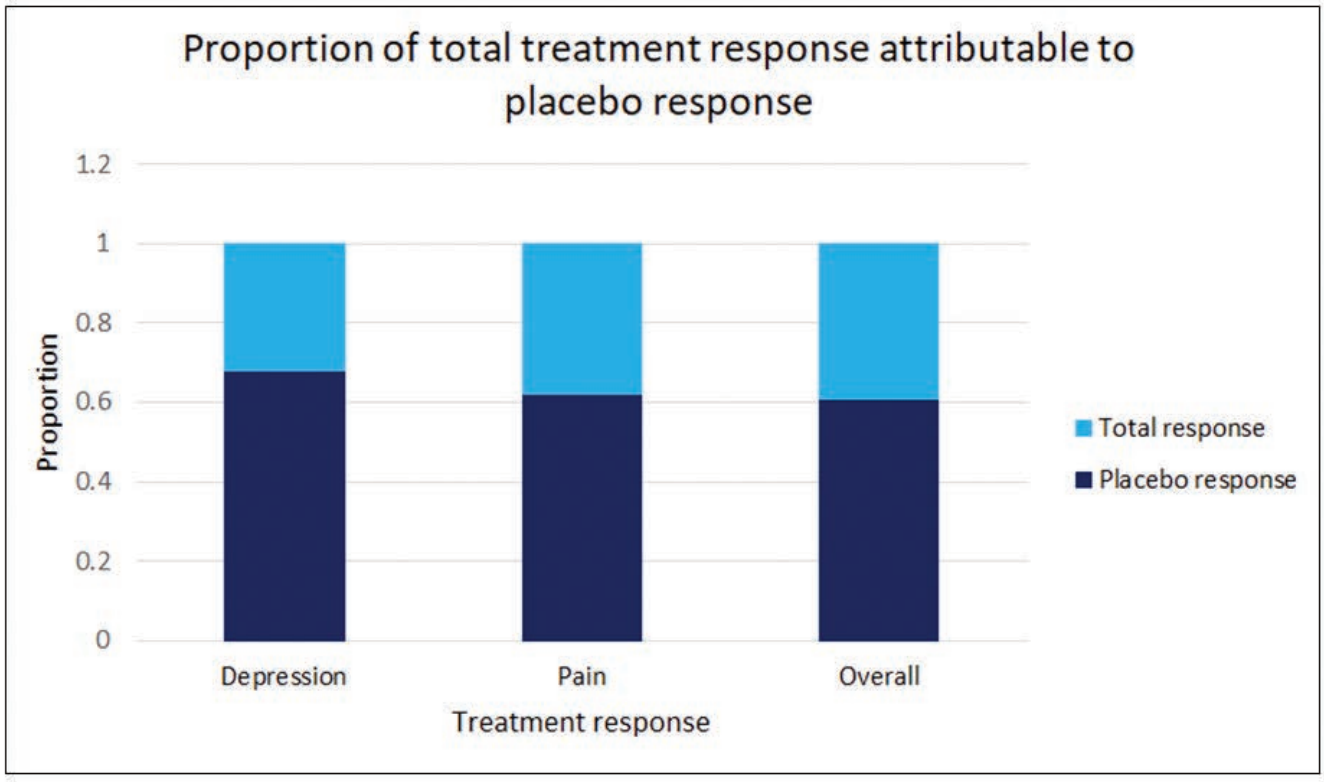
Approaches that reduce data variability would have a direct positive impact on the treatment effect size, resulting in ripple effects on the trial costs (fewer patients needed) and duration (less time needed to recruit patients). This approach has the added ethical benefit of exposing fewer patients to experimental drugs during clinical trials while improving success rates and effectively accelerating patient access to innovative treatments.

Reducing interpersonal data variability requires an understanding of the characteristics that differ between individual patients that relate to or explain their variable treatment response. Traditionally, clinical trials collect a wide range of biological, physical, or anatomic data – ranging from vital signs to the investigator's interpretation of patient disease status and/or improvement. We would, however, assert that patients are people and should be viewed holistically as having a unique personality, motivations, and beliefs. Acknowledging the industry is an era of patient centricity, understanding patient personality as a key component and an influencer of data variability would complete the full picture of patient data and only improve efficacy evaluation.

Understanding and reducing clinical data variability resulting from interpersonal differences would enable the field to understand the efficacy and potential of new therapies more quickly and effectively. Placebo response, for example, is one of the most significant sources of data variability in clinical trials, and it may account for a significant portion of the observed treatment effect (Figure 2).[7] Considering the contribution of the placebo response to clinical trial failures – and the fact that it has continued to increase in the past several decades despite the best efforts of scientists and physicians – the time is ripe to employ novel solutions. The placebo effect is a true psycho-social-biological phenomenon that is intrinsic to each patient and is influenced by the patient's individual personality, expectations, and beliefs – among other factors. This large diversity and quantity of data (like traits of personality) requires the use of new advanced data analytic methods. AI and ML can pinpoint the relevant variables and their relative importance and may simplify this complex information into a single patient characteristic: an individual score relating to each patient's placebo responsiveness. Integrating this information into clinical data analysis can yield substantial rewards: increased assay sensitivity, increased study power, improved success rates, and decreased sample size.

The financial impact of reducing clinical data variability can be equally impact-

FIGURE 2



A significant proportion of the total measured treatment response can be attributed to the placebo response in indications like pain and depression, as well as across clinical studies with pharmacological interventions.[7,13,14]

ful, relating to both decreased overall clinical development costs and earlier market launch. A Phase 3 patient cost may be as much as $40,000 per patient; thus, reducing sample size of a Phase 3, 1000 patient study by 30% could save about $12 million in direct costs and 3 months of recruitment time.[5] Considering that every month of a Phase 3 trial cost an average of $671,000, reducing timelines by 3 months would save about an additional $2 million.[8] Beyond this, an additional 3 months of marketing under patent protection may represent between $75 to $210 million in sales (depending on the drug). Similarly, reducing data variability may avoid or reduce the risk of an inconclusive trial - which avoids a minimum of 2 years of delay, clinical study and manufacturing costs, additional patients exposed to the study drug, and ultimately delayed sales. To better understand this, let's consider a case study employing these methods.

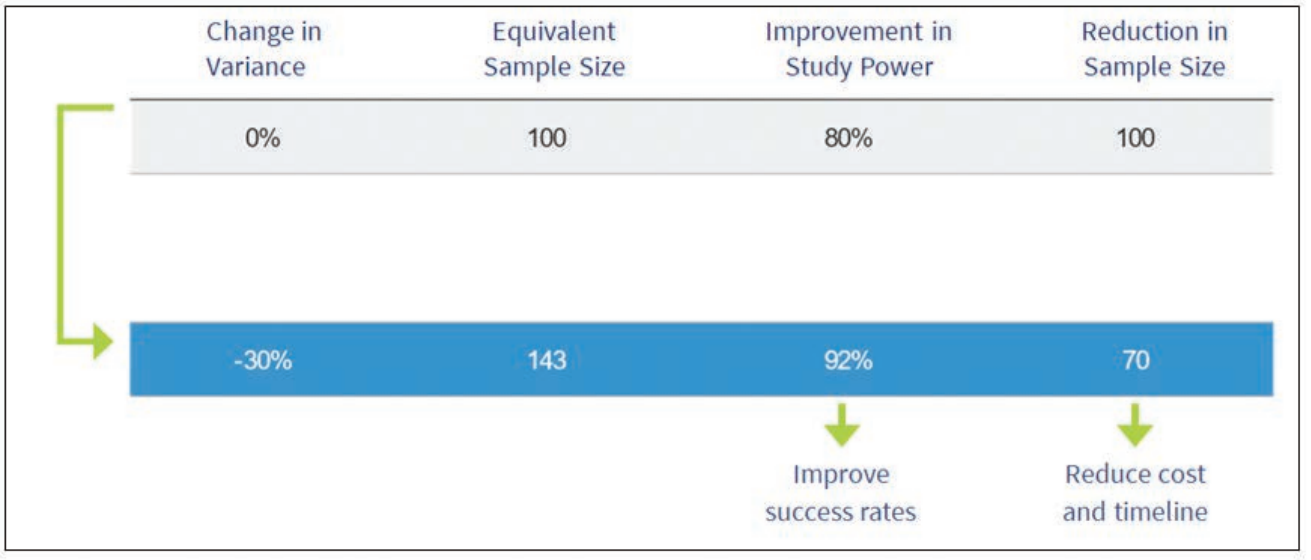
CASE STUDY: A PATIENT-CENTRIC APPROACH TO REDUCING THE IMPACT OF PLACEBO RESPONSE ON CLINICAL DATA ANALYSIS

We have used predictive algorithms based on machine learning to understand the spectrum of placebo responsiveness in a clinical trial patient population at baseline based on patient psychology, expectation, and other factors (eg, age, demographics, baseline disease intensity). This modeling approach is intended to address the inherent interpersonal differences in placebo response as a source of noise in the data with minimal trial burden and absolutely no added study risk. Including placebo responsiveness as a baseline covariate – as typically used by clinical trial statisticians to account for factors that differ between patients – can safely and significantly reduce data variability and improve study power.[9,10]

These machine learning-based models can be calibrated specifically for each disease and then used to calculate a single score for each patient in a given study. When used in the statistical analysis, the reduction in data variability improves the ability to detect true treatment efficacy. Currently, models have been constructed in multiple diseases with more than 10 clinical studies completed. Model performance has been consistent in chronic pain, Parkinson's disease, and ophthalmology (dry eye disease), with additional studies ongoing in areas like psychiatry, auto-immune disease, and neurology.[11,12] In general, it has been demonstrated to explain between 25%-35% of data variability related to the placebo response across endpoints and indications, regardless of route of drug administration and study design.

This ~30% reduction in placebo response-related data variability in indications evaluated to date can yield tremendous gains in study power and reduced enrollment. To illustrate this concept, one can consider a clinical trial with N=100 patients that is powered to 80% (Figure 3). Reduction in variance by 30%

FIGURE 3



The impact of reducing variability can be easily explained by considering a trial that has 100 patients and is powered to 80%. Reducing data variability by 30% yields equivalent study power to a trial that has 43% more patients or improves study power to 92%. Alternately, total trial enrollment can be reduced by 30% while maintaining study power.

translates into increasing study power from 80% to 92% - meaning the risk of trial failure due to false negative results is significantly decreased. Looking at this another way, the trial now has an equivalent power to a trial that included 43% more patients. Conversely, this same study now only requires 70 patients to achieve a power of 80%. Over time, use of such a covariate could result in reduced sample size in clinical trials, which quickly translates to reductions in clinical trial costs and timelines, and quicker delivery of drugs to market.

SUMMARY

The pharmaceutical industry sorely needs new approaches to improve efficiency of drug development to shorten timelines and reduce costs. Patients are complex beings with highly variable biological – and psychological – makeups, yet only biological characteristics have traditionally been considered when analyzing clinical trial data. Taking a more holistic, patient-centric approach by considering patients' individual psychology, perceptions, and beliefs provides drug developers the opportunity to quantify these interpersonal differences between patients and address this source of variability in data analysis and interpretation. In the example of the placebo response, new approaches powered by machine learning have been shown to successfully reduce data variability by 30% or more, which translates into increased success rates and decreased enrollment. These novel methods can provide substantial savings while improving market access of novel therapeutics. ◆

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BIOGRAPHIES

Dr. Dominique Demolle serves as Chief Executive Officer of Cognivia (formerly Tools4Patient) since its inception in 2013. She earned her PhD in Biochemistry from the University of Brussels. She joined the Clinical Research Group of GD Searle and then Eli Lilly. She has held positions with increasing leadership responsibilities at Eli Lilly and Company with the Lilly Indianapolis Clinical Research Unit in the US and the European Operational Staff management and ultimately became the Associate Director of Global Early Phase Operations. In 2007 she co-founded and successfully developed a Consulting Clinical Research Organization, including partnerships with pharma and biotech before she left to set up Cognivia with previous colleagues.

Dr. Erica Smith joined Cognivia (formerly Tools4Patient) as VP of Business Development in 2018 and assumed the role of Chief Business Officer in December, 2021. She earned her PhD in Biomedical Engineering from The University of Michigan in Ann Arbor, MI. She began her career in the pharmaceutical industry at Genetics Institute/Wyeth Research in Cambridge, MA, and Pfizer in Groton, CT. She then worked for several CROs, developing a strong track record of sales leadership, strategic planning, developing and executing corporate growth strategies, and marketing.

SYNTHETIC ANTI-INFECTIVES

Synthetic Polymers Offer a New Class of Anti-Infectives

By: James Graham

INTRODUCTION

Antimicrobial resistance (AMR) is the third leading cause of death worldwide – having estimated 4.95 million deaths associated with bacterial AMR in 2019, including 1.27 million deaths attributable to bacterial AMR.[1] As a result of persistent antibiotic use and hospital-acquired infections, the rapid emergence of AMR threatens our ability to treat common infections and support modern medicine.

AMR emerges naturally as an evolutionary response by microbes to avoid death. These resistance mechanisms are often encoded in the resistant microbe's DNA and are transferred to all daughter cells that can easily spread unchecked by current antibiotics, especially in hospital settings.

Most commonly, deadly hospital-acquired infections are a result of a group of bacteria known as ESKAPE pathogens that harbor multidrug-resistant properties that render existing antibiotics ineffective. Specifically, ESKAPE is an acronym that stands for six different commonly found multidrug-resistant pathogens: *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter* species. ESKAPE pathogens represent one of the biggest threats to modern medicine, and we desperately need an intervention.[2]

COMMON CLASSES OF ANTIBIOTICS & WHERE THEY FALL SHORT

Alexander Fleming revolutionized medicine by discovering modern-day penicillin in 1928. This discovery sparked the golden age of antibiotics, and 12 new classes of antibiotics were launched from 1935 to 1968.[3] However, after 1969, antibiotic discovery slowed, with only a handful of new classes discovered in the 50 years since.

With this drought of discovery, microbes have developed resistance, and physicians are often left with few tools to fight AMR for seemingly the most innocuous of infections. Below are some of the major classes of naturally derived antibiotics used today and their limitations when facing AMR.

Beta-lactams: This is the oldest documented antibiotic class and is composed of a number of antibiotics, including penicillin and cephalosporin derived from fungi. Beta-lactams work by inhibiting bacterial wall production and commonly cause several side effects. They have a broad spectrum of activity and are commonly utilized in dental, skin, respiratory tract, ear, kidney, bladder, urinary tract, and bone infections. Due to their extensive use over the decades, beta-lactams have significantly contributed to the emergence of ESKAPE pathogens.[4]

Tetracyclines: This antibiotic class is derived from Streptomyces bacteria from soil. Tetracyclines are broad-spectrum antibiotics most commonly used for rosacea and acne. They are bacteriostatic, meaning that they prevent bacteria from growing by inhibiting protein synthesis but do not necessarily kill them.

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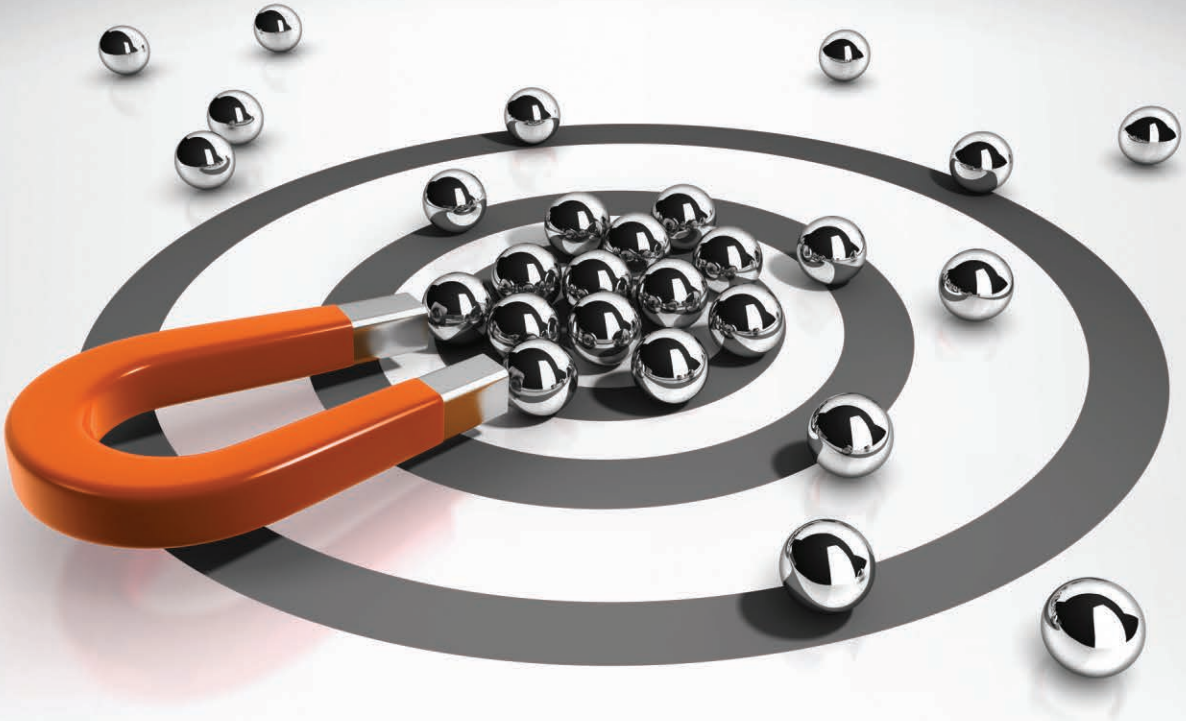

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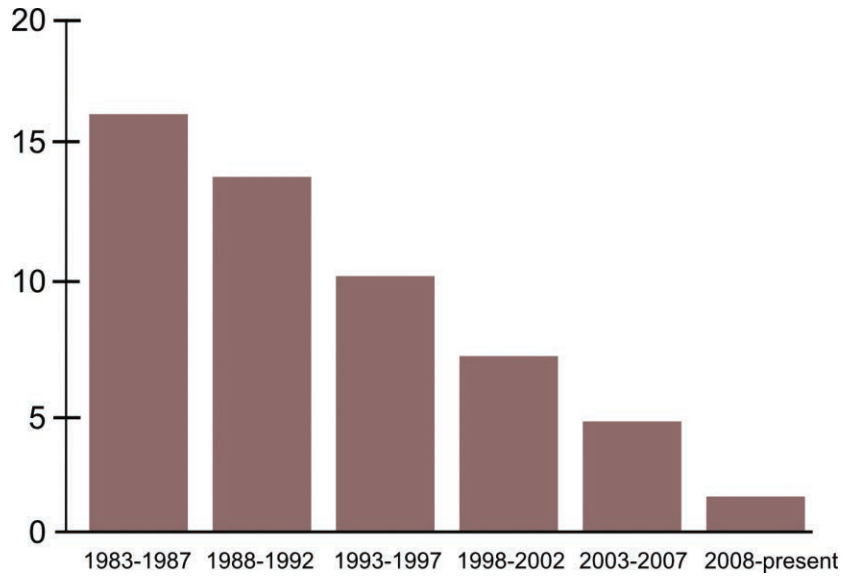
However, tetracyclines become toxic over time and can cause significant kidney damage. A diverse range of bacteria, including the ESKAPE pathogens, are quickly becoming resistant to this class of antibiotics.

Macrolides: This antibiotic class is also derived from soil-borne Streptomyces bacteria, and the most common type is erythromycin that can treat indications including pneumonia and skin infections. Macrolides are bacteriostatic, working similarly to tetracyclines by inhibiting protein synthesis without killing the bacteria. This class of antibiotics mainly act on Gram-positive bacteria and intracellular pathogens, and due to the high incidence of these types of infections, AMR is increasing against this drug class.

Aminoglycosides: This class is also derived from Streptomyces from the soil and is bactericidal, inhibiting bacterial protein synthesis. Aminoglycosides are used to fight Gram-negative bacteria across various disease indications and can be used in combination with other antibiotics. They can only be administered intravenously because the stomach breaks them down easily. This class can also cause severe kidney damage and irreversible damage to the ears. However, bacteria quickly become resistant to this class, and as such, aminoglycosides are considered a short-term antibiotic.

Following the first few decades of their discovery, antibiotics were highly effective, and physicians often prescribed them for use in infections, including nonbacterial infections.[5] This, along with extensive and unregulated use of antibiotics in agriculture in the US and across the world, has contributed to the emergence of AMR.[6]

FIGURE 1



The number of antibacterial approved by the United States Food and Drug Administration (FDA) has steadily declined over time.[15]

These traditional antibiotics kill bacteria or inhibit their growth by engaging a single target, acting within the bacteria or on the surface, and in many cases, the exposure of bacteria to a single target antibiotic leads to the development of AMR shortly after repeated use.

Despite the growing resistance, the global antibiotic pipeline remains deficient as most drugs advancing through the clinic are predominantly derivatives of well-established antibiotic classes and do not include any new class of molecules or new mechanisms of action.[7] The last time researchers discovered the most recent class of highly effective antibiotics was over 30 years ago, in 1987, and physicians are running out of tools to effectively treat bacterial infections.

To highlight this critical situation, a recent BIO industry analysis and evaluation of the current state of antibacterial research and development summarized the evolving crisis, "Although there have been 164 FDA-approved direct-acting antibacterial new chemical entities (NCEs) since the early 1900s, only one new molecular target NCE has been approved over the last 35 years, illustrating a need to broaden the antibacterial discovery engine. There have been 11 indirect-acting NCEs approved, including seven drugs that work to extend the activity of existing drugs and four monoclonal antibodies specific for exotoxins."[8]

The need for innovation is clear and unprecedented as the current pipeline for novel antibacterial drugs is still largely dependent on existing targets and will not address the burgeoning AMR crisis. Consequently, these startling dynamics make it imperative to drive investment into alternative approaches that have the potential to address these issues.

ADVANTAGES OF SYNTHETIC ANTI-INFECTIVES

Synthetic anti-infectives offer a potential solution to the obstacles encountered by naturally derived antibiotics in the constant arms race against AMR. Although synthetic anti-infectives are composed of

various unique classes, they all share a number of advantages.

Targeted Design: Synthetic antibiotics are designed with the end goal in mind. Scientists can engineer compounds to increase molecule specificity or enhance the binding of a chosen ligand, opening the possibility for compounds that can target key bacterial ligands efficiently.

Rapid Large-Scale Screening: When a synthetic compound is designed and produced at scale, its activity is screened against a range of drug targets, including those it was designed to target. Natural products contain inherently more structural diversity than synthetic compounds, and screening takes significantly longer to identify target sites. However, if the target is identified before the design in synthetic compounds, the screening process progresses much more quickly.

Efficient Manufacturing: Another notable advantage is that synthetic anti-infectives may be manufactured more efficiently than current antibiotics on the market. Traditional antibiotics are usually sourced from fungi or soil bacteria, relying on fermentation processes and large-scale bacterial culture followed by an extensive purification stage. On the contrary, the synthetic process gives rise to a 99.9% product yield in hours and requires no specialized and costly waste removal.

Cost-Effective: Natural antibiotics are often produced by organisms in exotic environments that are challenging to find and to grow in the lab, and the extensive time and effort it takes to search, source, and screen these compounds are costly. However, the design and development of synthetic anti-infectives can be extremely fast, spanning only a few days as compared to months or even longer for naturally sourced compounds.

BRINGING A NEW CLASS OF ANTI-INFECTIVES INTO THE CLINIC

Given the rapidly rising rates of AMR to various anti-infectives, it is imperative that additional treatment options are developed to avoid a future in which anti-infectives are entirely futile against pathogens, and Recce Pharmaceuticals is rising to the challenge. Recce is developing new classes of anti-infectives that hold the potential to resolve multidrug-resistant infections safely and effectively.

This new class includes RECCE© 327 (R327), a synthetic polymer designed to target a variety of infections caused by even the most resistant and difficult-to-treat bacteria. In March 2021, R327 was included in The Pew Charitable Trusts' list of Non-traditional Products in Development to Combat Bacterial Infections as the only clinical-stage new class of antibiotic in the world being developed for sepsis, the largest unmet medical need in human health.[9]

Independent studies undertaken by leading experts in bacteria Mechanism of Action (MoA) analysis have identified R327 to have a multi-faceted MoA: R327 permeabilizes cell membrane and enters the cell; R327 interrupts bacterial cellular energetics via ATP synthesis; cellular division and non-dividing cell functions are dis-

FIGURE 2

When exposed to R327, the outer membrane of *E. coli* cells are disrupted and can even burst at high concentrations.

"Given the rapidly rising rates of AMR to various anti-infectives, it is imperative that additional treatment options are developed to avoid a future in which anti-infectives are entirely futile against pathogens, and Recce Pharmaceuticals is rising to the challenge. Recce is developing new classes of anti-infectives that hold the potential to resolve multidrug-resistant infections safely and effectively."

rupted; R327 is rapidly and irreversibly bactericidal – and at high concentrations causes cell lysis.[10] Through this multi-layered MoA, R327 does not display any loss of efficacy against both Gram-positive and Gram-negative bacteria, including their multidrug-resistant superbug forms, even after repeated use[11] – a common failure associated with existing antibiotics. Most notably, current antibiotics rarely retain bactericidal activities against non-dividing or stationary phase bacterial cells; however, R327 showed remarkable activity against slow-growing bacteria, indicating potential antibacterial activity in biofilms.[10]

Recce has an automated manufacturing process, presently supporting clinical trials, that takes approximately an hour – producing 500 doses per automated manufacture output with a 99.9% product yield, allowing production to quickly and efficiently scale up to meet demand.[11]

Most importantly, Recce's anti-infectives can be administered intravenously, topically, nasally, orally, and inhaled to allow clinicians to use the most suitable formulation based on the type of infection and the patient's individual needs. Recce currently has two ongoing clinical programs: a Phase 1 intravenously administrated dose-escalation study in healthy subjects; and a topical administration in a Phase 1/2 trial of burn wound infections, including those caused by methicillin-resistant *Staphylococcus aureus* (MRSA) – one of the two most common healthcare-acquired infections.[12]

The Phase 1 intravenous safety study is an ascending dose, randomized, placebo-controlled, parallel, double-blind, single-dose study being conducted at Adelaide's CMAX clinical trial facility in Australia. This study is evaluating the safety and pharmacokinetics of R327 in healthy subjects, and so far, the interim data is promising. Upon successful completion of this trial, Recce will look to initiate a Phase 2 clinical trial in sepsis shortly thereafter. With 11 million sepsis-related deaths recorded and 48.9 million incident cases of sepsis recorded worldwide, there is a strong unmet need for a potent broad-spectrum anti-infective to treat this life-threatening infection without introducing toxicity or contributing to the rise of AMR.[1]

The topical Phase 1/2 infected burn wounds study is assessing the efficacy of R327 as a spray-on anti-infective for the treatment of burn wound infections across two dosing schedules at Fiona Stanley Hospital, Perth, Australia. The promising results thus far have shown broad-spectrum activity, with visible infection reduction within <24 hours and no adverse effects or abnormalities reported; even the chronic infections were cleared within 7 days. Patients with burn wounds often suffer severe bacterial infections that are painful, prevent wound healing, and can even result in death if not properly treated. Notably, many of these infections are resistant to most available antibiotics.[13]

In addition to Recce's current clinical trials, the team is actively assessing the efficacy of Recce's compounds, including R435, against other infectious diseases in preclinical studies. For example, *Helicobacter pylori (H. pylori)* is a bacterial infection in the stomach that causes peptic ulcers, and current antibiotic therapies are rapidly becoming ineffective due to the emergence of resistant strains. In preclinical studies, R435 has shown efficacy against *H. pylori* in a dose-dependent manner. Similar results have been observed for R327 in the treatment of multidrug-resistant *Streptococcus pneumoniae* and *Pseudomonas aeruginosa* in bacterial sinusitis.

In summary, when it is considered that, in the US alone, more than 2.8 million antibiotic-resistant infections occur each year, with more than 35,000 people dying as a result, the need for innovative broad-spectrum anti-infectives is imperative.[14] Synthetic anti-infectives offer unde-

niable benefits to address the global threat of AMR, and Recce is stepping up to provide potential solutions with their new class of synthetic anti-infectives designed to empower physicians with a broad-spectrum treatment option. With plans to continue developing R327 and additional compounds of the drug for other serious infectious diseases, the team will continue leveraging its versatile synthetic polymer to create further broad-spectrum anti-infectives to address the urgent global health threat posed by antibiotic-resistant superbugs. ◆

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BIOGRAPHY

James Graham is the Chief Executive Officer and Managing Director at Recce Pharmaceuticals. Prior to this he served 5 years as Executive Director and he has extensive experience in marketing, business development, and commercialisation of early-stage technologies with global potential. Under his leadership Recce Pharmaceuticals is on a growth path as an emerging global health leader in synthetic anti-infectives by pioneering the development and commercialisation of new classes of synthetic anti-infectives. James was the founding investor of Recce and to date has successfully raised USD $34 million for the Company.

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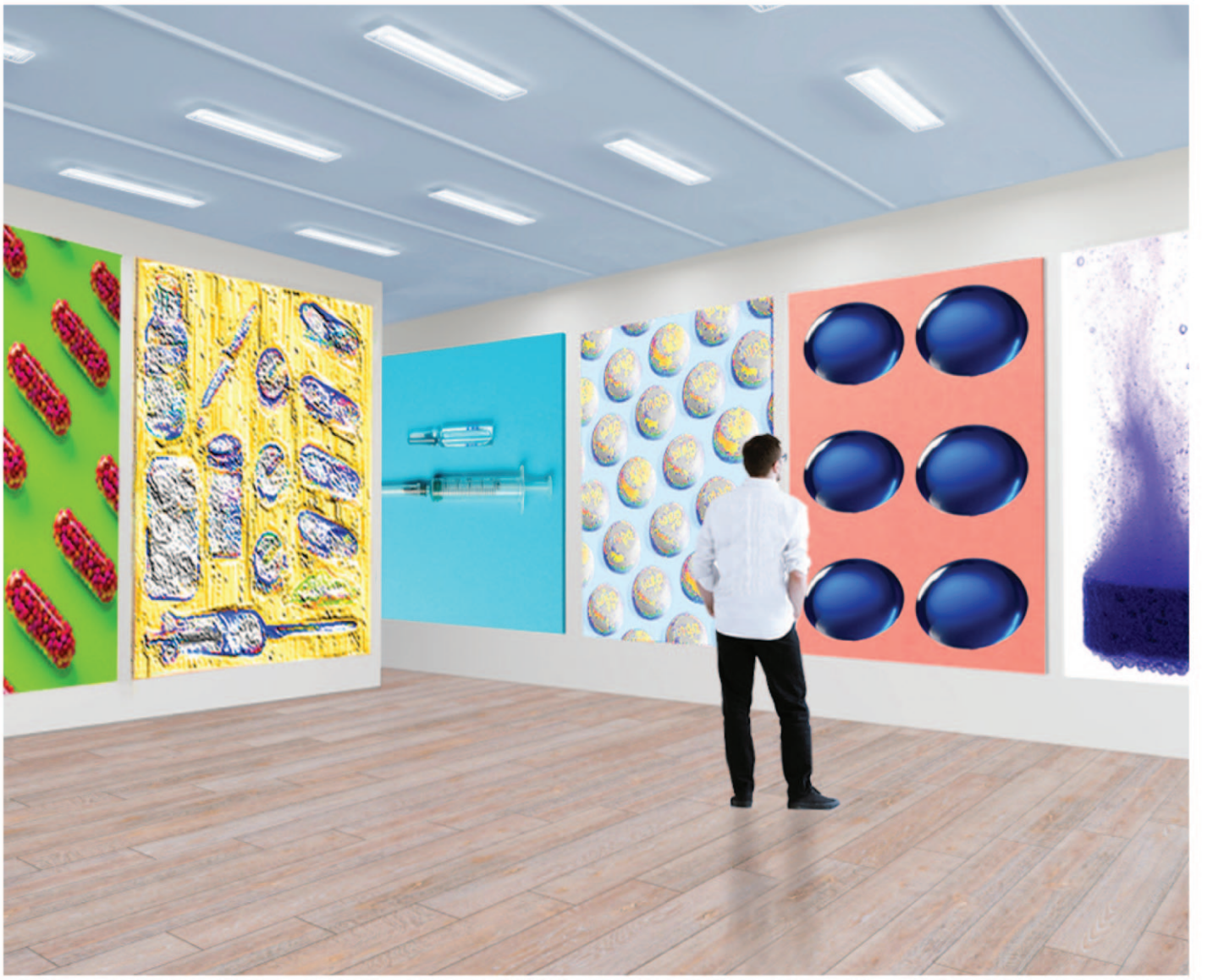

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