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Global Markets & Forecasts

The science & business of drug development in specialty pharma, biotechnology, and drug delivery

IN THIS ISSUE

INTERVIEW WITH **INSULET DELIVERY SYSTEMS GROUP'S** VP, BUSINESS DEVELOPMENT MICHAEL GRAFFEO

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Pharmaceutical Development White Noise & Dark Matter

Jeffrey Bacha, MBA
Chairman & CEO, DelMar Pharmaceuticals
The Importance of Strategic Collaborations With Universities & Organizations to Further Develop a Technology

Finn Bauer, PhD
Director of R&D & Head of Solid Formulations, MilliporeSigma
Alternative Technologies to Overcome Solubility & Bioavailability Challenges

Scott Brown, MS
Executive Director, Device Development, Merck
Avoiding the Pitfalls in Device Development & Commercialization

Nila Das, PhD
Senior Research Investigator, Bristol-Myers Squibb
Antibody-Drug Conjugates & Their Unique Challenges

Martin Eastgate, PhD
Director, Chemical & Synthetic Development, Bristol-Myers Squibb
Design, Development & Implementation of New Routes to Promising Clinical Candidates

Mahen Gundecha, MBA
Head of Alliance Management, Sandoz Inc. (Novartis Group)
Building Alliance Management Into a Value-Enhancing Capability Throughout Your Organization

Tom Johnson
Senior Director, Life Science Solutions, Exostar
$(SI)^2$ - Pairing Scientific Innovation With Security Innovation

Conrad F. Mir
President & CEO, Calmare Therapeutics
Dilution or Death? The Cost of Just One More Day in the Microcap World

Kurt Nielsen, PhD
President, Lupin
Indispensable Principles of Rx & Gx Product Selection & Portfolio Management: Debunking Myths & Demystifying the Decision-Making

Peter Pekos, MSc
President & CEO, Dalton Pharma Services
Form, Fit & Function: All Are Critical for Drug Development Success With a CDMO

Mathias Romacker, MA
Senior Director, Device Strategy, Pfizer
Global Market Trends for Injection Devices – A Brief Overview

Laurie Smaldone, MD
COO & CSO, NDA Group AB
How Integrated Global/Market Access Drug Development Strategies Add Value in Early Development

Ronald L. Smith, PhD
Scientific Assoc. VP, Pharmaceutical Sciences, Merck Research Laboratories
Transformative Innovations in Drug Product Science & Technology

Cornell Stamoran, PhD
Vice President, Strategy for Catalent, Inc., & Co-Chair, Catalent Applied Drug Delivery Institute
The Patient-Focus Imperative: Formulating & Delivering Better Patient Outcomes

Lilli Zakarija, MSME, MBA
Co-Founder/President, EdgeOne Medical
Device Design Controls When the Combination Product Uses an Off-the-Shelf Device Versus Custom Developed Device

Acute Coronary Syndrome Market

"GlobalData estimates sales of ACS therapeutics in 2015 to be approximately $7.8B across the seven major markets (7MM), which are the US, the five major European markets (5EU: France, Germany, Italy, Spain, and UK), and Japan. In the 2015 base year, 10% of market share was attributed to acute-phase sales ($714M) and 90% to the chronic phase ($7B). By 2025, GlobalData expects the ACS market to grow at a strong Compound Annual Growth Rate (CAGR) of 4.6%, reaching sales of $12.1B by the end of the forecast period."

Table of Contents

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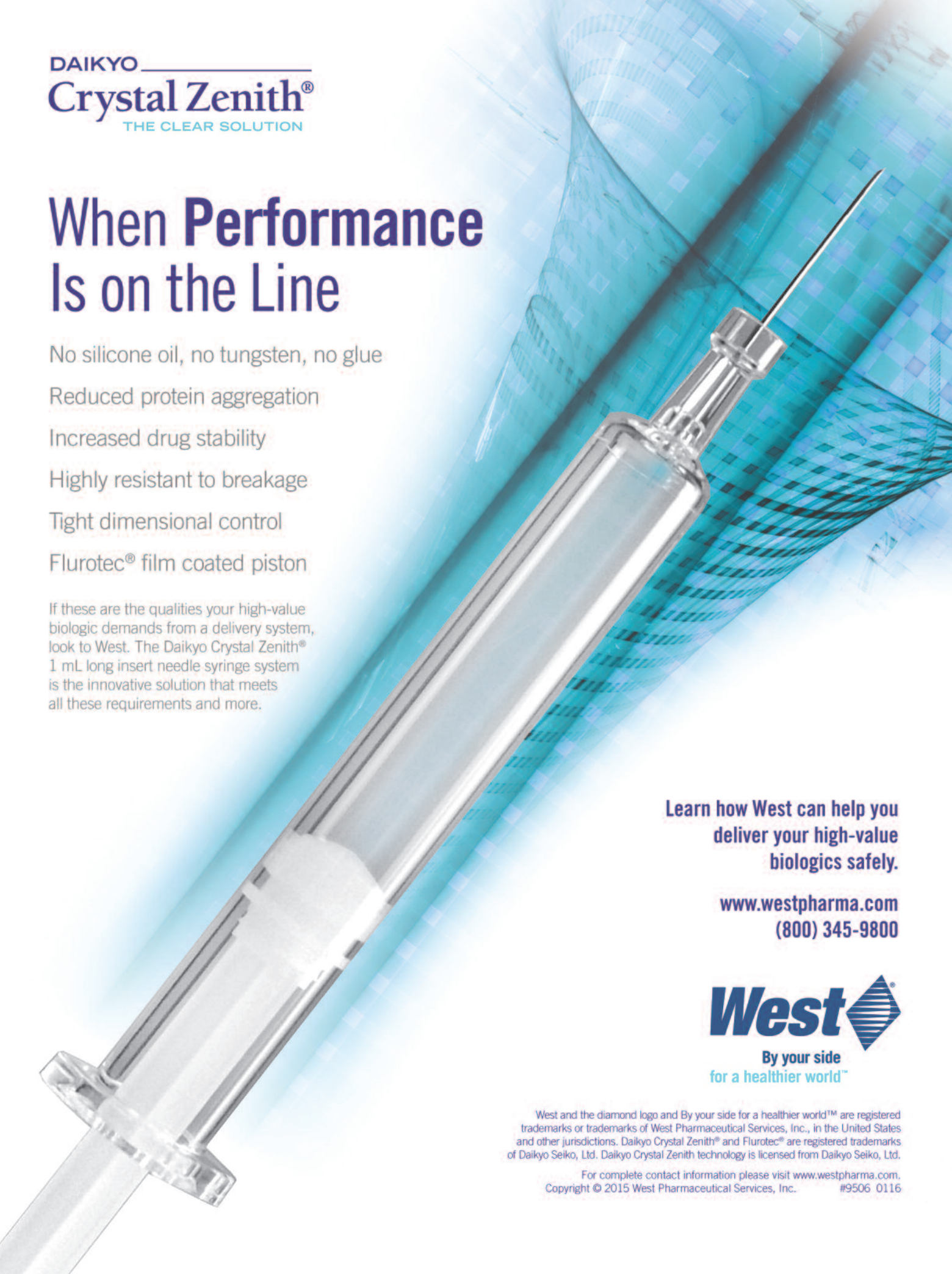

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Protein Therapeutics Market

"The global market for protein drugs reached $174.7 billion in 2015. At a 5-year compound annual growth rate (CAGR) of 7.3%, it is predicted to attain $248.7 billion by 2020. By region, the United States is the largest market, valued at nearly $92 billion in 2015. The United States is also the fastest-growing, and with a projected 5-year CAGR of 10.9%, the revenue for this region is forecast to be $154.1 billion by 2020. Europe, which reached $42.2 billion in 2015, is expected to total $48.1 billion by 2020, reflecting a 5-year CAGR of 2.6%."

p.44

Table of Contents

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Pluristem Signs Term Sheet for $30-Million Equity Investment Agreement

Pluristem Therapeutics Inc. recently announced it has signed a term sheet for an investment of approximately $30 million by China-based Innovative Medical Management Co., Ltd., a publicly listed Chinese Company active in the healthcare industry and an affiliate of Zheshang Venture Capital Co., Ltd. ZSVC has ¥ 30 billion yuan ($4.45 billion) under management through more than 30 venture capital, private equity, angel, and buyout funds.

The term sheet has been approved by Innovative Medical's Board of Directors and is subject to its shareholders' approval, which is expected to occur on or about November 9, 2016. Upon the approval of Innovative Medical's shareholders, the term sheet will become binding. Pursuant to the term sheet, approximately 16,890,000 shares of Pluristem common stock will be sold at $1.77 per share. In addition, Pluristem will issue to Innovative Medical approximately 4,422,500 warrants to purchase shares of Pluristem's common stock with an exercise price of $2.50 per warrant, exercisable for a period of 5 years. The shares will be subject to a lock up agreement for 6 months after the closing of the agreement. In accordance with the term sheet, Innovative Medical will have one seat on Pluristem's Board of Directors for as long as it holds at least 12.5% of Pluristem's issued and outstanding stock. Innovative Medical will also have certain information, registration, and pre-emptive rights as well as certain negotiation rights with respect to potential transactions of Pluristem in China.

The parties plan to enter into definitive agreements no later than December 26, 2016. Until the earlier of December 26, 2016 or the entry into the definitive agreements, Pluristem has agreed not to enter into any agreement or arrangement regarding equity financing of the company at a common stock price per share equal to or less than $2.20, without the prior written consent of Innovative Medical.

The securities, which may be sold in the proposed private placement, have not been registered under the Securities Act of 1933, as amended, or state securities laws and may not be offered or sold in the United States absent registration with the Securities and Exchange Commission (SEC) or an applicable exemption from such registration requirements. Pursuant to the term sheet, Pluristem has agreed to file a registration statement with the SEC registering the resale of the shares of common stock purchased in the private placement and the shares of common stock underlying the warrants.

Innovative Medical Management Co., Ltd was founded in September 2003. The company completed an IPO and listed on the Shenzhen Stock Exchange on September 25, 2007. Its main business is a combination of healthcare service, hospital management, scientific research, and pearl culture and design. Innovative Medical owns three major hospitals in China: Qiqihar Jianhua Hospital, Zhejiang Haining Kanghua Hospital and Jiangsu Futian Rehabilitation Hospital. These hospitals have more than 2,100 professional staff and 2,300 clinical beds.

ZSVC is one of the most active venture capital firms in China. Company executives have extensive industrial and managerial experience, as well as a deep understanding of private equity investments. A leading investment management firm in China, Zheshang Venture Capital (ZSVC) was founded in November 2007, and is headquartered in Hangzhou, with offices in Beijing, Shanghai, Shenzhen, Shenyang and San Francisco. In November 2015, ZSVC became a publicly listed company in China.

Pluristem Therapeutics Inc. is a leading developer of placenta-based cell therapy products. The company has reported robust clinical trial data in multiple indications for its patented PLX (PLacental eXpanded) cells and is entering late-stage trials in several indications. The cell products release a range of therapeutic proteins in response to inflammation, ischemia, hematological disorders, and radiation damage. PLX cell products are grown using the company's proprietary three-dimensional expansion technology. They are off-the-shelf, requiring no tissue matching prior to administration.

Pluristem has a strong intellectual property position; company-owned and operated, GMP-certified manufacturing and research facilities; strategic relationships with major research institutions; and a seasoned management team.

BIOPHYTIS Chooses Patheon to Produce Clinical Batches

BIOPHYTIS recently announced it has entered into an agreement with US firm Patheon for the industrial scale-up and manufacturing of clinical batches, the first stage of the Phase IIB clinical trial for drug candidate Macuneos in AMD (age-related macular degeneration).

Macuneos is a drug candidate against the dry form of AMD: AMD affects the central part of the retina, called the macula, causing severe visual impairment and irreversible loss of central vision beyond 60 years old. Macuneos protects retinal pigment epithelium: BIOPHYTIS has shown in animal models a protection of retinal cells against phototoxic effects of A2E in the presence of blue light (oxidative stress), a reduction in accumulation of A2E, and eventually a slowdown of the degenerative process of the retina.

As part of the agreement, Patheon will be in charge of the industrial scale-up and manufacture of Macuneos clinical batches. These lots will be used by BIOPHYTIS for the Phase IIB study MACA, to be launched in Europe and the United States once all approvals of regulatory authorities have been obtained.

"We are very pleased to outsource the production of Macuneos to such an internationally recognized actor. This is the first stage of the MACA clinical program dedicated to treat dry AMD, a pathology with no therapeutic solution on the market so far. Our whole team is dedicated to the success of the MACA clinical project, a strategic axis of development for BIOPHYTIS," said Stanislas Veillet, CEO of BIOPHYTIS.

The MACA Phase IIB trial will involve 300 patients over 50 years of age with intermediate dry form of AMD, and should involve 20 centers in Europe and 10 in the United States. Patients enrolled in the study will be divided into three cohorts: Macuneos 100 mg, Macuneos 350 mg, and placebo. The investigation period will be 18 months, with an intermediate checkpoint after 9 months.

The study will begin with a preparatory phase, including a pharmacokinetics and safety study will be conducted in Europe among healthy elderly volunteers (the MACA-PK study), and a pilot characterization study of the target population and a preselection of patients suffering from dry AMD in major recruitment centers in Europe and the US (the MACA-OBS study).

BIOPHYTIS SA, founded in 2006, develops drug candidates targeting diseases of aging. Using its technology and know-how, BIOPHYTIS has begun clinical development of innovative therapeutics to restore the muscular and visual functions in diseases with significant unmet medical need.

Proteon Therapeutics Announces Overview of Phase I Clinical Program

Proteon Therapeutics, Inc. recently announced that an overview of the company's Phase I clinical program of investigational vonapanitase in peripheral artery disease (PAD) was presented at the 28th Transcatheter Cardiovascular Therapeutics (TCT) conference, the annual scientific symposium of the Cardiovascular Research Foundation, in Washington, DC.

The presentation, titled Arterial Dilatation with Recombinant Human Elastase: A Novel Approach to Treating Peripheral Vascular Disease, was given by Dr. Ehrin J. Armstrong, Associate Professor, Medicine-Cardiology at University of Colorado School of Medicine and Director, Interventional Cardiology VA Eastern Colorado Healthcare System.

"Current treatments for patients with PAD have poor long-term durability in alleviating clinical symptoms," said Dr. Armstrong. "Proteon's innovative approach with vonapanitase has the potential to provide an important new option for patients suffering from PAD."

Dr. Armstrong discussed the company's two planned Phase I clinical studies evaluating vonapanitase, a recombinant human elastase. These multicenter, dose-escalation studies will evaluate the safety and technical feasibility of a single administration of vonapanitase as a monotherapy and as an adjunct to angioplasty for patients with PAD. The company expects to initiate both studies in 2016.

Patients with peripheral artery disease (PAD) of the lower extremities experience stenosis, or blockage, in the arteries providing blood to the legs. These patients typically present with exercise-induced leg pain, a condition known as intermittent claudication. Symptoms of claudication include impaired walking function as patients quickly experience leg pain that can be resolved only through rest. In advanced cases of PAD, known as critical limb ischemia, a severe lack of blood flow causes leg pain at rest, which can result in gangrene or tissue death and the need for amputation. Current revascularization procedures to address PAD are often ineffective and lack durability, resulting in ongoing suffering for patients. PAD is a global problem affecting a large and growing number of people in developed and developing countries. An estimated eight to 12 million Americans are affected by PAD.

Vonapanitase (formerly PRT-201) is an investigational drug designed to treat vessel injury response that leads to blockages in blood vessels and reduced blood flow. Vonapanitase is applied in a single administration and is currently being studied in two Phase III clinical trials, PATENCY-1 and PATENCY-2, in patients with chronic kidney disease (CKD) undergoing surgical creation of a radiocephalic arteriovenous fistula (AVF) for hemodialysis. Proteon previously completed a Phase I clinical trial with vonapanitase in patients with PAD. Vonapanitase has received fast track and orphan drug designations from the US FDA, and orphan medicinal product designation from the European Commission, for hemodialysis vascular access indications.

Sedia Biosciences & Floragenex Announce Completion of Merger

Sedia Biosciences Corporation and Floragenex Inc. recently announced the merger of their companies. Details of the transaction were not disclosed. Sedia will continue the business of Floragenex as a wholly owned subsidiary with current Floragenex Chief Executive Officer, Dr. Rick Nipper, continuing oversight of the new subsidiary.

Floragenex, Inc., a genomics testing service provider focused on next-generation DNA sequencing, was founded in 2007 as a spin out of the University of Oregon, while Sedia Biosciences, founded in 2009, develops and commercializes point of care diagnostics in human diseases, including HIV. The combined company will continue to provide genomic services for scientific customers and testing solutions for HIV and other infectious agents.

"The merging of Sedia and Floragenex creates a compelling strategic transaction for our combined shareholders and the capability to deliver leading-edge technological innovation to our current and future customers," said Roger Gale, Chairman and Chief Executive Officer, Sedia Biosciences. "The merger will also yield many synergies and benefits in the months and years ahead. Specifically, it will strengthen and diversify our scientific capability across both immuno- and molecular (DNA) diagnostic technologies; broaden our potential product range; expand access to the plant and animal kingdom markets; accelerate development of next generation products; and strengthen sales and marketing, business development, and strategic planning."

Dr. Ronald Mink, President and Chief Sciences Officer of Sedia Biosciences, noted "The medical diagnostics market has rapidly developed intense interest in the application of molecular biology technology to novel point-of-care testing approaches. The pooled expertise of both companies will assist Sedia's expansion into novel molecular diagnostic products to supplement and enhance our current product lines, and allow further expansion into plant and animal testing. There is tremendous potential in the synergistic opportunities afforded Sedia as a result of our combined expertise and markets."

Sedia Biosciences Corporation is a US-based healthcare company focused on the development and commercialization of novel in vitro diagnostic and epidemiological tests, including the Sedia LAg-Avidity EIA and BED HIV-1 Incidence EIA. The company is dedicated to advancing access to medical care by developing innovative diagnostic and monitoring products that enable more cost effective and expanded testing for infectious diseases and other conditions. Based in Portland, OR, Sedia develops, manufactures, licenses, and sells in vitro diagnostic and epidemiological tests as well as specimen collection devices.

Merus Receives Milestone Payment from Ono Pharmaceutical

Merus N.V., a clinical-stage immuno-oncology company developing innovative bispecific antibody therapeutics, recently announced that the company received an undisclosed milestone payment from Ono Pharmaceutical Co., Ltd. (Osaka, Japan, Ono), under the ongoing collaboration between the two companies. The milestone was triggered as a result of preclinical confirmatory studies using the selected lead bispecific antibody candidate that Ono intends to advance into clinical testing. Ono and Merus have also extended their collaboration by signing an additional agreement for CMC activities to be carried out by Merus.

"Our research partnership with Ono continues to move ahead of schedule and yield promising results demonstrating the broad applicability of our Biclonics platform," said Ton Logtenberg, PhD, Chief Executive Officer of Merus. "This proprietary technology, which generates full-length human IgG antibodies, allows for the rapid identification of bispecifics with functionality that is superior to conventional monoclonal antibodies. We are delighted that our work with Ono has resulted in the generation of a therapeutic candidate for autoimmune and related diseases that warrants further evaluation in a clinical setting, and we look forward to developing additional innovative therapeutics with this world-class partner."

In April 2014, Merus and Ono executed a research and license agreement to jointly develop bispecific antibody therapies in autoimmune diseases. In April 2015, Merus received a milestone payment for achieving preclinical proof-of-concept with a lead bispecific antibody.

Merus is a clinical-stage immuno-oncology company developing innovative full- length human bispecific antibody therapeutics, referred to as Biclonics. Biclonics are based on the full-length IgG format, are manufactured using industry standard processes and have been observed in preclinical studies to have several of the same features of conventional monoclonal antibodies, such as long half-life and low immunogenicity. Merus' lead bispecific antibody candidate, MCLA-128, is being evaluated in a Phase I/II clinical trial in Europe as a potential treatment for HER2-expressing solid tumors. Merus' second bispecific antibody candidate, MCLA-117, is being evaluated in a Phase I/II clinical trial in patients with acute myeloid leukemia. The company also has a pipeline of proprietary bispecific antibody candidates in preclinical development, including MCLA-158, which is designed to bind to cancer stem cells and is being developed as a potential treatment for colorectal cancer and other solid tumors, and Biclonics designed to bind to various combinations of immunomodulatory molecules, including PD-1 and PD-L1.

Renova Therapeutics Strengthens Gene Therapy IP Estate With Latest Patent License

Renova Therapeutics recently announced it has obtained an exclusive worldwide license to a urocortin 3 gene patent from the nonprofit Research Development Foundation (RDF). The patent expands the intellectual property estate of the company, which has previously obtained a license agreement for RDF's patent portfolio of stresscopin and urocortin genes and peptides, paving the way for its paracrine gene therapy product pipeline.

RDF and Renova Therapeutics have entered into a worldwide exclusive license agreement for RDF's patent of the urocortin 3 gene and uses thereof. Renova Therapeutics plans to research this therapeutic gene with the intent to create paracrine gene therapy treatments for sufferers of cardiovascular diseases, such as heart failure, a key therapeutic area for the company.

"Securing rights to the urocortin 3 gene is instrumental to our cardiovascular paracrine gene therapy development pipeline," says Jack W. Reich, PhD, CEO and Co-founder of Renova Therapeutics. "Just as we have seen astonishing preclinical results with urocortin 2 gene transfer for type 2 diabetes, we've seen favorable physiological effects in preclinical models of urocortin 3 gene transfer in heart failure."

Heart failure afflicts more than 28 million people globally and is the only cardiovascular disease that is increasing in prevalence. It is the most common cause for emergency hospital admissions in patients 65 and older. Paracrine gene therapy is a non-invasive method intended to substantially improve patient outcomes in chronic diseases, such as heart failure.

Renova Therapeutics' paracrine gene therapy treatments are based on a novel systemic approach that introduces therapeutic genes capable of directing the body's cells to work more normally. This proprietary approach exploits the use of peptide genes that possess favorable cardio-metabolic effects via their paracrine activity. This single-IV-injection treatment method is a foundation for future products that have the potential to bring about permanent improvements in heart failure and type 2 diabetes patients.

With a worldwide exclusive license secured, one or more of Renova Therapeutics' paracrine gene therapy product candidates may comprise the urocortin 3 gene.

Renova Therapeutics is developing definitive, one-time gene therapies and peptide infusion treatments to restore the health of people suffering from chronic diseases. The first indications the company is pursuing are gene therapy treatments for congestive heart failure (CHF) and type 2 diabetes, two of the most common and devastating chronic diseases in the world. The company's lead product, RT-100, is a treatment that delivers a therapeutic gene directly to the heart during a routine outpatient procedure and has the potential to increase heart function in millions of patients with CHF.

CymaBay Therapeutics Announces Newly Issued US Patent for the Treatment of NAFLD & NASH

CymaBay Therapeutics, Inc. recently announced that the US Patent and Trademark Office has issued US Patent No. 9,381,181. This patent provides coverage to at least 2035 and claims methods of treating NAFLD and NASH comprised of orally administering a therapeutically effective amount of MBX-8025.

MBX-8025 is a potent and selective agonist of PPAR-δ, a nuclear receptor important for lipid transport, storage, and metabolism in liver and muscle. In a Phase II study in subjects with mixed dyslipidemia, MBX-8025 decreased LDL-C, triglycerides and high sensitivity CRP, a biomarker of inflammation. MBX-8025 also decreased alkaline phosphatase and gamma glutamyl transferase, two key markers of cholestasis. In a recently completed Phase II study in subjects with primary biliary cholangitis (PBC), MBX-8025 decreased markers of cholestasis and inflammation without appearing to cause pruritus while also lowering LDL-C. CymaBay has also completed a pilot Phase II clinical study showing that MBX-8025 lowers LDL-C in patients with homozygous familial hypercholesterolemia (HoFH). The US FDA has granted CymaBay orphan drug designation for MBX-8025 as a treatment for HoFH and Fredrickson types I and V hyperlipoproteinemia.

NASH is a severe type of non-alcoholic fatty liver disease (NAFLD) that is associated with obesity, insulin resistance, and type-2 diabetes and is characterized by the accumulation of fat in the liver. NASH occurs when the accumulation of liver fat is accompanied by inflammation and cellular damage. The inflammation can lead to fibrosis (scarring) of the liver and eventually progress to cirrhosis, portal hypertension, liver cancer, and eventual liver failure. Once the disease advances beyond NASH to these life-threatening conditions, liver transplantation is the only alternative.

CymaBay Therapeutics, Inc. is a clinical-stage biopharmaceutical company focused on developing therapies to treat metabolic diseases with high unmet medical need, including serious rare and orphan disorders. MBX-8025 is a potent, selective, orally active PPAR-δ agonist. A Phase II study of MBX-8025 in patients with mixed dyslipidemia established that it has an anti-atherogenic lipid profile. CymaBay has completed Phase II studies for MBX-8025 in subjects with primary biliary cholangitis and homozygous familial hypercholesterolemia, establishing proof-of-concept in both indications. Arhalofenate, CymaBay's other product candidate, is a potential Urate-Lowering Anti-Flare Therapy that has completed five Phase II studies in subjects with gout. Arhalofenate has been found to reduce painful flares in joints while at the same time lowering serum uric acid by promoting excretion of uric acid by the kidney. This dual action addresses both the signs and symptoms of gout while managing the underlying pathophysiology of hyperuricemia.

Gamida Cell Receives FDA Breakthrough Therapy Designation for NiCord

Gamida Cell recently announced that the US FDA has granted Breakthrough Therapy Designation to the company's lead product candidate, NiCord, in development as a novel graft modality for bone marrow transplantation in patients with high risk hematological malignancies (blood cancers), such as leukemia and lymphoma. The international, multi-center Phase III registration study of NiCord is planned to begin before the end of the year.

Breakthrough therapy designation may be granted to a drug that is intended to treat a serious or life-threatening condition, and where preliminary clinical evidence indicates that the drug may demonstrate substantial improvement on at least one clinical significant endpoint over available therapies. A breakthrough therapy designation entitles the company to more intensive FDA guidance on an efficient and accelerated drug development program, and eligibility for other actions to expedite the FDA review, such as a rolling submission and priority review.

"We are very pleased the FDA has recognized the potential of NiCord to address the unmet clinical need in bone marrow transplantation," said Dr. Yael Margolin, President and CEO of Gamida Cell. "The breakthrough therapy designation creates the foundation for a joint and concerted effort between the FDA and Gamida Cell to bring this important therapy faster to patients. We look forward to continuing our close cooperation with the FDA and other regulatory agencies to a positive conclusion as we prepare for commercialization."

Data from the Pilot, and Phase I/II studies of NiCord to date, have demonstrated clinically meaningful improvement in time to neutrophil engraftment over cord blood transplantation. Additionally, NiCord study data have shown fewer infections, reduced length of hospitalization, quicker platelet engraftment, and improved non-relapse mortality when compared to unmanipulated cord blood transplantation. Click here to review the results presented at ASCO 2016 and here for the data presented at EBMT 2016.

Gamida Cell is a world leader in cellular and immune therapies for the treatment of cancer and orphan genetic diseases. The company's pipeline of products are in development to treat a wide range of conditions, including cancer; genetic hematological diseases, such as sickle cell disease and thalassemia; and bone marrow failure syndromes, such as aplastic anemia, genetic metabolic diseases, and refractory autoimmune diseases. Gamida Cell's current shareholders include Novartis, Elbit Imaging, Clal Biotechnology Industries, Israel Healthcare Venture, Teva Pharmaceutical Industries, Denali Ventures, and Auriga Ventures. For more information, visit www.gamida-cell.com.

Catalent Biologics & Triphase Accelerator Corporation Announce License Agreement to Advance SMARTag

Catalent and Triphase Accelerator Corporation recently announced that Triphase will obtain worldwide rights to further develop Catalent's proprietary CD22-4AP Antibody-Drug Conjugate (ADC), which has been developed by Catalent's wholly owned subsidiary, Redwood Bioscience, Inc., using its SMARTag technology platform.

Catalent will receive an upfront payment and has the potential to earn additional development and commercial milestone payments, plus a royalty on product sales. Triphase will also contract with Catalent for development, manufacturing and analytical services to support a fast path to clinic.

CD22-4AP is a novel, site-specific ADC, targeting CD22, a B-cell restricted sialoglycoprotein that is an important modulator of B-cell signaling and survival, which is expressed on 90% of B-cell malignancies. CD22 is a clinically validated ADC target with potential in Non-Hodgkin's Lymphoma (NHL) and Acute Lymphoid Leukemia (ALL). Catalent's ADC, CD22-4AP, is a site-specific modified humanized antibody conjugated to a toxin payload using Catalent's proprietary Hydrazino-Pictet-Spengler (HIPS) chemistry and proprietary 4AP linker.

Preclinical data has shown that this optimization of payload placement and linker composition, combined with the stability afforded by HIPS chemistry, leads to better tolerability and expanded therapeutic index.

"Given our deep experience in investigating potential treatment for blood cancers and oncology clinical drug development, it is a logical progression for us to explore other approaches for other hematologic tumors. We believe in the potential of Catalent's SMARTag technology and look forward to advancing CD22-4AP to clinical proof of concept studies," said Dr. Mohit Trikha, Chief Scientific Officer, Executive Vice President and Head of R&D at Triphase.

"Triphase has demonstrated expertise and a track record in advancing preclinical oncology candidates to clinical proof of concept," added Mike Riley, Catalent Biologics' Vice President & General Manager. "We look forward to leveraging Triphase's expertise in combination with our proprietary SMARTag technology and supporting infrastructure to bring this potentially transformational treatment to patients."

The proprietary SMARTag site-specific protein-modification and linker technologies were developed by Redwood Bioscience to enable the generation of homogenous bioconjugates engineered to enhance potency, safety, and stability. The technology employs natural post-translational modifications found in human cells to create one or more aldehyde tags at designated sites on protein molecules. These chemical "handles" are then stably conjugated to payloads (eg, cytotoxic or effector) to prevent their systemic release. The SMARTag platform provides precise payload positioning, stable, site-specific conjugation and defined stoichiometry of drug-protein ratios. The control afforded by the technology enables identification of superior drugs from libraries of differentially designed conjugates. Catalent acquired Redwood Bioscience in 2014.

Dipexium Receives European Medicines Agency Designation as a Small & Medium Enterprise

Dipexium Pharmaceuticals, Inc. recently announced it has been granted Small and Medium Enterprise (SME) designation by the European Medicines Agency (EMA). The company recently completed its pivotal Phase III clinical trials (OneStep-1 and OneStep-2) with Locilex in mild infections of diabetic foot ulcers in the US under a Special Protocol Assessment (SPA) agreement from FDA. Dipexium expects to have top-line data from these trials available for release shortly as its scientific advisory team is finalizing the database, which currently remains blinded.

The SME designation was established by EMA to promote innovation and the development of new medicinal products by smaller companies. Companies with SME status are eligible to receive financial incentives as well as administrative and regulatory support through national and regional level programs. These benefits include access to dedicated EMA personnel during the clinical development process as well as reductions in fees associated with regulatory procedures, such as Scientific Advice, Marketing Authorizations, and inspections.

"We are pleased to have SME designation, which allows us to benefit from financial incentives and support from the EMA as we aim to bring Locilex to the global pharmaceutical marketplace," said David P. Luci, President and Chief Executive Officer of Dipexium. "With prior guidance from the EMA, the results from our clinical trials conducted in the US will form the basis for the planned Marketing Authorization Application to be submitted shortly after filing our New Drug Application Amendment with the FDA."

OneStep-1 and OneStep-2 were identical, double-blind, placebo-controlled clinical trials conducted simultaneously that enrolled a total of 389 patients at 59 separate centers in the US. The primary objective was to establish the clinical superiority and safety of topical Locilex plus standard local wound care as compared to placebo cream plus standard local wound care, in the treatment of Mild DFI. Patients were randomized 1:1 to receive either topical Locilex plus standard local wound care or placebo cream plus standard local wound care for 14 days, with final evaluation at day 28. The primary endpoint of the trials is clinical response, which is defined as infection resolved per the judgment of each treating physician using the 2012 Infectious Disease Society of America (IDSA) Clinical Practice Guideline for the Diagnosis and Treatment of Diabetic Foot Infections. Secondary endpoints include microbiological success, which is defined as complete microbiological response, as well as the incidence and severity of adverse events. Other clinical endpoints include several measurements with respect to the timing to, and the extent of, wound healing. The FDA has agreed to a Special Protocol Assessment (SPA) with Dipexium for Locilex's pivotal Phase III clinical trial program in Mild DFI.

Daiichi Sankyo & Inspirion Delivery Sciences Announce Licensing Agreement

Daiichi Sankyo, Inc. and Inspirion Delivery Sciences LLC recently announced the companies have entered into a strategic collaboration agreement in the US to commercialize FDA-approved MorphaBond (morphine sulfate) extended-release tablets, CII. The agreement also provides Daiichi Sankyo, Inc. with the rights to commercialize a separate investigational Inspirion compound in the US, if approved by the US FDA. Both MorphaBond and the second product feature SentryBond, a unique, patent-protected abuse-deterrent technology.

MorphaBond (morphine sulfate) extended-release tablets, CII is an abuse-deterrent opioid indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative options are inadequate.

Under the terms of the agreement, which is pending Hart-Scott-Rodino clearance, Inspirion will receive an upfront payment, in addition to milestone payments and royalties. Daiichi Sankyo will lead the commercialization of the co-promotion with Inspirion for MorphaBond, and if approved, the second product.

MorphaBond is an abuse-deterrent formulation of extended-release morphine using physical and chemical barriers, without the use of aversive agents or opioid antagonists. MorphaBond is formulated with inactive ingredients that make the tablet more difficult to adulterate for misuse and abuse while maintaining extended-release characteristics even if the tablet is subjected to physical manipulation and/or chemical extraction.

Relative to morphine sulfate extended-release tablets, these properties of MorphaBond increase resistance to cutting, crushing, or breaking using a variety of tools. When subjected to a liquid environment, the manipulated MorphaBond formulation forms a viscous material that resists passage through a needle.

MorphaBond was developed in accordance with the FDA Guidance on Abuse-Deterrent Opioids. MorphaBond has been tested in vitro using methods of manipulation that drug abusers commonly use for preparation of extended-release opioids for administration by various routes, including oral consumption, intranasal insufflation, injection, and smoking. Overall, data from the Category 1 through Category 3 in vitro and in vivo studies suggest that MorphaBond has properties that are expected to reduce abuse or misuse via injection or insufflation; however, abuse by these routes is still possible.

"Our goal is to become a leader in the pain therapeutic area and to be known as a company that is focused on the needs of patients and committed to being part of the solution to prescription drug abuse," said Ken Keller, President, Administrative and Commercial at Daiichi Sankyo, Inc. "MorphaBond is a valuable addition to the growing pain franchise at Daiichi Sankyo and will offer healthcare providers with a new option as part of a comprehensive approach to treating pain while fighting against the potential for abuse."

"The FDA approval, this collaboration, and the joint commercialization of MorphaBond with Daiichi Sankyo are major milestones for Inspirion," added Stefan Aigner, MD, CEO of Inspirion. "Daiichi Sankyo is a leader in the US pharmaceutical market and has established a substantial presence in the opioid market. Inspirion is excited to be collaborating together on the launch of MorphaBond."

Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, physicians should reserve MorphaBond for use in patients for whom alternative treatment options (eg, non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain. MorphaBond is not indicated as an as-needed (prn) analgesic.

MorphaBond should be prescribed only by healthcare professionals who are knowledgeable in the use of opioids for the management of chronic pain.

The SentryBond technology platform combines inactive excipients with active pharmaceutical ingredients in a tablet that is specifically designed to frustrate abuse via various methods of manipulation and routes of administration. When subjected to physical manipulation and/or attempts at chemical extraction, SentryBond is designed to maintain the intended release profile of extended-release products and to delay the release of immediate release products. Inspirion's technology imparts its abuse-deterrent characteristics via physical and chemical methods, without the use of antagonist or aversive agents. SentryBond technology is covered by an issued US patent, with multiple US and global patent applications pending.

Cellectar Biosciences Announces USPTO Issues Formal Patent Allowance

Cellectar Biosciences, Inc. recently announced that the United States Patent and Trademark Office (USPTO) has issued a formal patent allowance for CLR 1603, which covers method of use for the treatment of a variety of solid tumors and associated cancer stem cells using the company's phospholipid drug conjugate (PDC) delivery platform technology with paclitaxel. This patent allowance follows the May 2016 issuance of the composition of matter patent for the same compound.

CLR 1603 is a form of paclitaxel conjugated to the company's patented phospholipid drug conjugate delivery platform using a simple compound linker. The USPTO patent allowance covers method of use for breast, pancreatic, lung, colorectal, and prostate cancers. The company expects the full patent to be granted by the end of 2016.

"The receipt of this formal patent allowance represents the fourth time Cellectar has secured a positive USPTO action since May 2016. These actions have expanded and strengthened our intellectual property portfolio for PDC delivery platform assets, including our lead therapeutic product candidate CLR 131 and our chemotherapeutic conjugate program assets," said Jim Caruso, President and CEO of Cellectar. "While we continue to aggressively protect our products through strategic intellectual property achievements, we remain committed to advancing an intelligent research and development program to further optimize asset valuation."

Cellectar's product candidates are built upon its patented cancer cell-targeting delivery and retention platform of optimized phospholipid ether-drug conjugates (PDCs). Its phospholipid ether (PLE) carrier platform was deliberately designed to be coupled with a variety of payloads to facilitate both therapeutic and diagnostic applications. The basis for selective tumor targeting of our PDC compounds lies in the differences between the plasma membranes of cancer cells compared to those of normal cells. Cancer cell membranes are highly enriched in lipid rafts, which are glycolipoprotein microdomains of the plasma membrane of cells that contain high concentrations of cholesterol and sphingolipids, and serve to organize cell surface and intracellular signaling molecules. PDCs have been tested in over 70 different xenograft models of cancer.

Cellectar Biosciences is developing phospholipid drug conjugates (PDCs) designed to provide cancer targeted delivery of diverse oncologic payloads to a broad range of cancers and cancer stem cells. Cellectar's PDC platform is based on the company's proprietary phospholipid ether analogs. These novel small-molecules have demonstrated highly selective uptake and retention in a broad range of cancers. Cellectar's PDC pipeline includes product candidates for cancer therapy and cancer diagnostic imaging.

ACS MARKET

Acute Coronary Syndrome Market 2015-2025

By: Michela J. McMullan, PhD, GlobalData's Analyst covering Cardiovascular & Metabolic Disorders

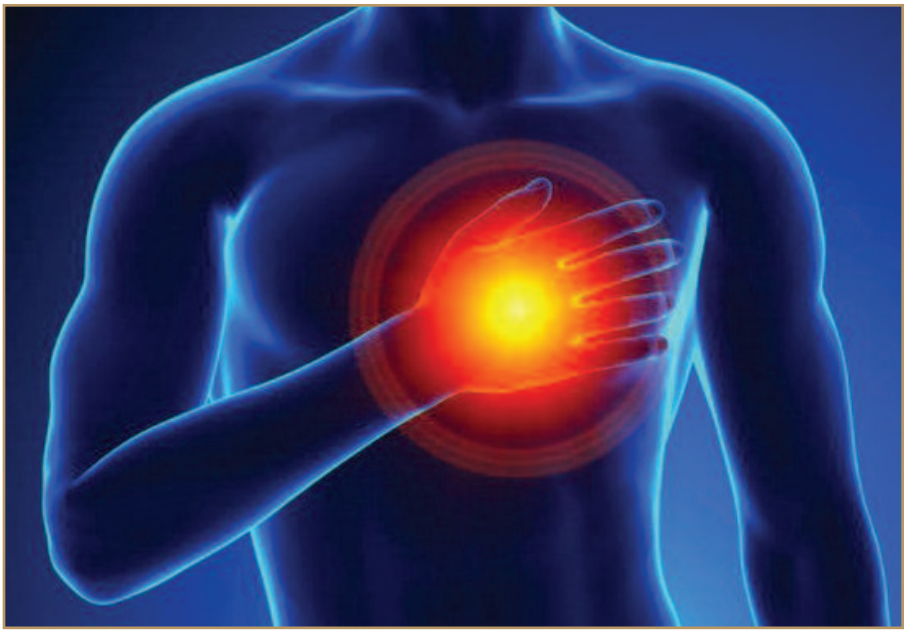
INTRODUCTION

Cardiovascular disease (CVD), including ischemic heart disease and stroke, is the leading cause of mortality in the world. The term acute coronary syndrome (ACS) applies to a spectrum of acute CVD states that are precipitated by coronary artery occlusion that results in ischemia and the necrosis of myocardial tissue. In the most modern use of the term, ACS strictly refers to a range of ischemic cardiovascular events that includes unstable angina (UA), myocardial infarction (MI), and/or death due to myocardial ischemia. In general, ACS can be viewed as the culmination of coronary artery disease (CAD), the asymptomatic build-up of atherosclerotic plaque on the walls of the coronary arteries. An ACS event is initiated upon plaque rupture triggering platelet activation and the coagulation cascade to form a thrombus on the wall of the artery that restricts blood flow. The triggering of an ACS event stemming from UA or MI initiates the acute-phase treatment setting, where therapeutic interventions are utilized to reverse and prevent the physiochemical processes that lead to coronary stenosis. The chronic-phase treatment setting, by contrast, involves secondary preventative measures that are used to prevent recurrent ACS events. The ACS therapeutic space is well-established and boasts a plethora of branded and generic drug choices to treat the major conditions associated with ACS: thrombosis (fibrinolytics, anticoagulants, and antiplatelets), hypercholesterolemia/atherosclerosis (statins and PCSK9 inhibitors), and hypertension (renin angiotensin aldosterone system [RAAS] inhibitors and beta blockers). Due to the broad range of sub-indications and available drug targets, it is evident that the ACS market is a highly lucrative area for pharmaceutical companies to invest into drug development.

THE ACS MARKET

GlobalData estimates sales of ACS therapeutics in 2015 to be approximately $7.8B across the seven major markets (7MM), which are the US, the five major European markets (5EU: France, Germany, Italy, Spain, and UK), and Japan. In the 2015 base year, 10% of market share was attributed to acute-phase sales ($714M) and 90% to the chronic phase ($7B). By 2025, GlobalData expects the ACS market to grow at a strong Compound Annual Growth Rate (CAGR) of 4.6%, reaching sales of $12.1B by the end of the forecast period. This is mainly attributed to the chronic-phase growth, which is forecast to reflect a CAGR of 5%, reaching $11.4B in sales by 2025 (94% of market share). Over this forecast, the most prominent wave of sales increase comes from the proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor class, which is expected to reach $2.5B in global sales by 2025 for ACS. The launch of ETC-1002, the first-in-class lipid-lowering adenosine triphosphate-citrate lyase (ACL) inhibitor/adenosine monophosphate-activated protein kinase (AMPK) activator, is another key driver of ACS market growth, as sales are projected to peak at $767M by 2025. Moreover, an increase in the global prevalence of ACS will also cause a growth in sales, as the total ACS population in the 7MM is anticipated to reach 32,440,271 people by 2025, which represents an annual growth rate of 1.8% from 2015.

THERAPEUTIC LANDSCAPE



The launch of new drugs in the ACS space in the 5 years preceding 2015 has mostly impacted the antiplatelet arena. The most welcome additions to the antiplatelet arsenal were the new-generation antiplatelets, AstraZeneca's Brilinta (ticagrelor), and Eli Lilly/Daiichi Sankyo's Effient (prasugrel), which are now the two central pillars of dual antiplatelet therapy (DAPT) regimens. Brilinta, in particular, is expected to continue a robust increase in global annual sales, peaking in 2019, prior to its US patent expiry, at approximately $940M. Brilinta is positioned favorably in the first half of this forecast due to its expected launch in Japan by 2017 and its proven superiority to cornerstone antiplatelet clopidogrel. Moreover, Brilinta is the first antiplatelet approved for use longer than 1 year post-MI, and its direct competitor, Effient, is contradicted in certain high-risk patients, allowing Brilinta to maintain an excellent clinical and commercial position. It is worth noting that the most prominent barrier that will restrict the growth of the ACS market during the forecast period is the loss of patent exclusivity of these new-generation antiplatelets, Brilinta and Effient, in all 7MM by 2025. More recent antiplatelet approvals included the launches of The Medicines Company's Kengreal (cangrelor) and Merck's Zontivity (vorapaxar), which highlights the push in development toward antiplatelet therapeutics before 2015.

Of the numerous pathologies that manifest in the ACS population, the current late-stage pipeline is composed exclusively of lipid-altering drug candidates. As ACS is a culmination of CAD triggered by the long-term build-up of atherosclerotic plaques, lipid-altering agents that address the root cause of CAD — the cholesterol-rich coronary plaques — are among the most essential strategies for the long-term preventative treatment of ACS. Indeed, the future growth of the ACS franchise relies entirely on drugs that treat hypercholesterolemia/atherosclerosis.

The pipeline collection of promising candidates includes four major groups, three of which are first-to-market classes that are all vying for market share as adjunct therapies to the standard-of-care (SOC) statins, and for statin-intolerant patients. There are two first-in-class CETP inhibitors in the Phase II/III pipeline, Merck's anacetrapib and Amgen's AMG-899. However, given that three CV giants have terminated their CETP-inhibition programs in recent years, Pfizer's torcetrapib (2006), Roche's dalcetrapib (2012), and Eli Lilly's evacetrapib (2015), no key opinion leader (KOL) interviewed by GlobalData showed any confidence in either drug's chance of approval. There are two PCSK9 inhibitors, Pfizer's bococizumab and Eli Lilly's LY3015014, in Phase II/III development. Based on the trial progression, bococizumab will likely be the third PCSK9 inhibitor to market, followed by LY3015014, after the marketed Repatha (evolocumab) and Praluent (alirocumab). Two reconstituted human apolipoprotein A-1 (apoA-1) analogs are also in the Phase II pipeline, Cerenis Therapeutics' CER-001 and CSL Limited's CSL-112. KOLs believe these therapies may be useful for niche high-risk patients that have repeated re-infarctions, yet the cost and formulation (infusion) will limit use from the entire ACS population. Lastly, Esperion's truly innovative ACL inhibitor/AMPK activator, ETC-1002, is entering Phase III development in 2016 as a low-density lipoprotein cholesterol (LDL-C) lowering therapy. KOLs believe ETC-1002 may become the SOC for statin intolerance in the future based on its current clinical profile.

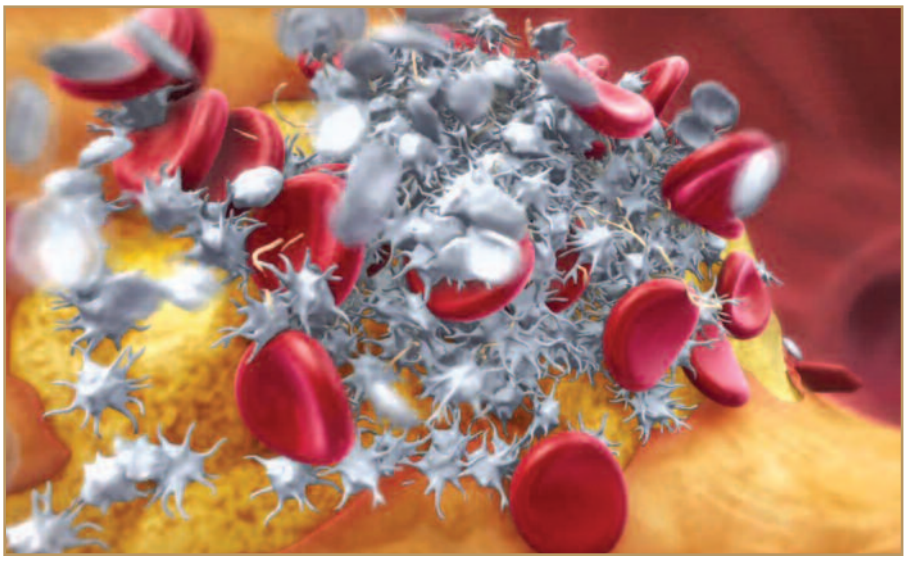
The statin market represents a critical barrier to achieving blockbuster status for any of these lipid-lowering drugs. All of them will be prescribed as second-line treatments to statins, in cases of intolerance, or as adjunct treatment for patients who need additional lowering of LDL. Moreover, late in 2013, new cholesterol treatment guidelines established by the American College of Cardiology Foundation (ACCF) and American Heart Associa-

"Real opportunities exist in the ACS arena due to the launch of the revolutionary PCSK9 inhibitors, Repatha and Praluent, in 2015. According to KOLs, a large proportion of patients with clinical atherosclerotic CVD cannot reach guideline-recommended levels of LDL-C with the SOC therapies, which leads to primary or recurrent ACS events. However, these game-changing therapies both truly demonstrated their efficacy in lowering LDL-C in their pivotal Phase III trials, showing a 57% and 58% reduction in LDL-C from baseline compared to placebo for evolocumab and alirocumab, respectively."

tion (AHA) recommended the use of statins, and only statins, for the effective treatment of high LDL-C in ACS patients. The real-world impacts of these guidelines will play out over time, but they are likely to represent a major hurdle for up-and-coming LDL-C drugs in the ACS pipeline. In general, GlobalData believes the current ACS pipeline is relatively weak, as of the seven pipeline contenders, two of the therapies are "me-too" drugs within the PCSK9 family, yielding suboptimal innovation, and four of the drugs directly target high-density lipoprotein cholesterol, the "'HDL-C hypothesis," which has so far not been deemed a successful strategy in improving CV outcomes.

Real opportunities exist in the ACS arena due to the launch of the revolutionary PCSK9 inhibitors, Repatha and Praluent, in 2015. According to KOLs, a large proportion of patients with clinical atherosclerotic CVD cannot reach guideline-recommended levels of LDL-C with the SOC therapies, which leads to primary or recurrent ACS events. However, these game-changing therapies both truly demonstrated their efficacy in lowering LDL-C in their pivotal Phase III trials, showing a 57% and 58% reduction in LDL-C from baseline compared to placebo for evolocumab and alirocumab, respectively. So far, the major barrier for adoption is the price of these therapies; however, once CV outcomes data for MI prevention is shown (throughout 2017), KOLs stressed that uptake will be significantly accelerated in ACS patients. Moreover, the two other PCSK9 inhibitors in the ACS pipeline, bococizumab and LY3015014, may offer further benefits to patients in terms of price and frequency of administration, respectively. The growth of the PCSK9 class, among others in the ACS pipeline, also highlights the current expansion of biologics into the ACS mainstream.

The revolutionary innovations in CV drug development in recent years cannot be denied, yet despite this and due to a persistent aging population in the 7MM, many key unmet needs exist. First, elderly patients are frequently under-represented in ACS clinical trials, leading to a lack of



clinical understanding of how to treat this population segment effectively and safely. GlobalData KOLs agreed that for the entire ACS population, notable progress has been seen, yet clinical trials are focused on low-risk patient segments under the age of 75, which is a significantly smaller portion of the whole ACS patient population as the average age of primary ACS is 68 years. On a similar note, although improvements in secondary prevention of ACS have reduced the rates of mortality and morbidity in this space, repeated infarctions lead to left ventricle dysfunction, causing post-ACS patients to develop heart failure (HF). GlobalData KOLs stated that the majority of their post-ACS patients die of this comorbidity. Unfortunately, to date, no small molecule, biologic, or cell therapy has shown notable efficacy in repairing the infarcted myocardium or improving left ventricle ejection fraction to prevent HF. The last key clinical unmet need that was emphasized by all of GlobalData's KOLs was the development of a blood-thinning agent with reduced bleeding risk; this is especially sought-after for elderly patients. However, while pushing for improved antithrombotic efficacy, as in the new generation of antiplatelets and anticoagulants, there will be an increase in patients' bleeding risk as it is tied to the same mechanism. As such, KOLs were virtually unanimous in their skepticism that this goal is achievable. As the current state of the marketed and pipeline products stands, no therapy addresses these unmet needs, which will certainly stunt market growth as new therapies with sub-optimal efficacy improvements struggle to enter the already crowded ACS scene.

OUTLOOK

Although the ACS market is set to grow at a CAGR of 4.6%, reaching $12.1B by 2025, the potential for the market to be even more lucrative exists, especially in the sizable lipid-targeting arena. An evident trend in the ACS pipeline is the targeting of the HDL pathway. Low levels of HDL are known to be a major independent risk factor for atherosclerotic CV disease, yet specifically raising HDL is without precedent and has yet to be proven as a long-term outcome-based benefit for ACS and related events. From KOL interviews, it is increasingly evident that treating hypercholesterolemia is dependent on an array of other factors that go beyond cholesterol control by increasing HDL and lowering LDL. These other factors include the thickness of the coronary plaque, a drug's effect on inflammatory markers, its pleiotropic role, and its ability to lower LDL-C at the cellular level, which could entirely eliminate atherosclerosis. Innovation at this level is currently lacking in the lipid-lowering ACS pipeline, where achieving this scientific leap will require companies to look beyond the canonical avenues of ACS pathology to revolutionize the current landscape. This will be the determining factor toward the positive progression of the ACS market in the future. ◆

GlobalData's report PharmaPoint: Acute Coronary Syndrome – Global Drug Forecast and Market Analysis to 2025 (published August 2016) and other relevant topics are available at www.globaldata.com.

To view this issue and all back issues online, please visit www.drug-dev.com.

BIOGRAPHY

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HCV MARKET

Recent Success in HCV Treatment Brings Relief to Patients but Challenges to Companies

By: Mirco Junker, PhD, Analyst covering Infectious Diseases at research and consulting firm GlobalData

INTRODUCTION

Driven by several novel regimens recently receiving approval in the US and in Europe, high cure rates exceeding 90% are now achievable for most patients suffering from chronic hepatitis C. As a result of this unprecedented success, the industry is reaching a new phase in the fight against this deadly infectious disease. The pressure is now shifting to the healthcare providers to determine if the future of hepatitis C treatment will include a (near) eradication in the developed world, or if hepatitis C will remain a debilitating and life-threatening factor in our society.

HEPATITIS C TREATMENT LANDSCAPE

The treatment of chronic infections caused by the hepatitis C virus (HCV) has undergone a dynamic shift in recent years. Historically, treatments were based on interferon, which was subsequently replaced by peginterferon, administered in combination with ribavirin. Although these treatments were able to achieve cure rates of over 50% in some patient groups, they were also associated with severe adverse events (AEs) and long treatment durations of nearly a year under close supervision by a physician. The development of the first direct-acting antiviral (DAA) ushered in a new era, in most cases reducing the severity and frequency of AEs, shortening and simplifying treatments, while simultaneously increasing efficacy. The first-generation DAAs included Vertex's Incivek (telaprevir) and Merck's Victrelis (boceprevir), both NS3/4A inhibitors, which launched in the US for genotype 1 (GT1) patients in 2011. However, the main breakthrough came in 2013 with the approval of the first NS5B inhibitor, Gilead's Sovaldi (sofosbuvir). Gilead followed up on the success it achieved with Sovaldi with the launch of Harvoni (a fixed-dose combination of sofosbuvir and ledipasvir, an NS5A inhibitor). The ability to cure over 95% of many patient populations, simultaneously shortening treatment durations to 12 weeks with a once-daily single pill, while also eliminating peginterferon and ribavirin for most patients, truly revolutionized the hepatitis C treatment paradigm.

Together, Sovaldi and Harvoni helped to position Gilead as the unquestionable market leader in the 9 major markets (9MM: US, France, Germany, Italy, Spain, UK, Japan, China, and Brazil), providing the pharmaceutical giant with global revenues of $19.1 billion in 2015 alone. However, other companies did not remain on the sidelines. Bristol-Myers Squibb (BMS) is currently represented in all major markets, with Daklinza (daclatasvir) in the US and Europe as well as with Daklinza and Sunvepra (asunaprevir) in Japan, BMS' most important market. Janssen, the pharmaceutical arm of Johnson & Johnson, is currently represented by Olysio (simeprevir). Despite having efficacious products in these markets, both BMS and Janssen have struggled for market share against Gilead in the past 2 years, mostly due to the fact that the two main recommendations used by physicians globally, AASLD and EASL, include Olysio and Daklinza only in combination with Sovaldi or with Sovaldi and ribavirin, thereby opening the door for Gilead to use differential pricing of Sovaldi and Harvoni. By providing Harvoni at a 12.5% list price premium over Sovaldi, Gilead has as much as eliminated the margin for other market participants relying on co-administration with Sovaldi, making Harvoni the drug of choice for the important GT1 patient group.

Additional competition has also come from AbbVie and Merck. Both companies provide a Sovaldi-independent DAA regimen for patients infected with either GT1 or GT4. Although Ab-

bVie's Viekira Pak (paritaprevir, ritonavir, ombitasvir, +/- dasabuvir) was already approved in 2014, it struggled to gain market share as the drug required different treatment approaches for the different GT1 subgroups, GT1a and GT1b, and required a twice-daily administration of multiple pills, compared to Harvoni's single-tablet, once-daily administration. AbbVie's hope for that to change in the next months will be based on the recent FDA approval for a once-daily formulation, Viekira XR. On the other hand, Merck has rebounded from the failure of Victrelis, launching its new DAA regimen Zepatier (grazoprevir/elbasvir) successfully this year in the US and in Europe, and Zepatier is now poised to be one of the major DAA regimens for patients with GT1 and GT4 during the next years. Despite these various attempts to break Gilead's dominance during the past 2 years, these multi-faceted disadvantages for Daklinza, Olysio, and Viekira Pak have resulted in a lopsided situation in which Gilead's competitors achieved a combined market share in the US of about 10% in 2015, although Merck's Zepatier might the first non-Gilead DAA reaching double-digit market share in the coming years.

Despite this success of the pharmaceutical industry in addressing the major unmet needs in the HCV field, not all patient groups profited equally from these advances. The initial focus of the industry was on DAA regimens curing patients infected with GT1, the most prevalent GT in the 9MM. Until this year, GT2 and GT3 patients proved more problematic to treat, and cure rates lagged behind those of GT1 patients. In addition, several other patient groups were still waiting for their medical needs to be met, including patients with comorbidities like kidney or renal failure, patients co-infected with HIV and/or hepatitis B, and patients relying on other medication with significant drug-drug-interactions (DDIs) with the DAAs.

TABLE 1

Current & Future DAA Treatment Options			
Main Currently Marketed DAAs			
Drug Name (Molecule)	**Company**	**Therapy Class**	**Most Advanced Development Stage (Region)**
Daklinza (daclatasvir)	BMS	NS5A inhibitor	Marketed (US, EU, Japan, Brazil)
Epclusa (sofosbuvir/velpatasvir)	Gilead	NS5B nucleotide polymerase inhibitor; NS5A inhibitor	Marketed (US, EU)
Harvoni (sofosbuvir/ledipasvir)	Gilead	NS5B nucleotide polymerase inhibitor; NS5A inhibitor	Marketed (US, EU, Japan)
Olysio (simeprevir)	Janssen	NS3/4A protease inhibitor	Marketed (US, EU, Japan, Brazil)
Sovaldi (sofosbuvir)	Gilead	NS5B nucleotide polymerase inhibitor	Marketed (US, EU, Japan, Brazil)
Viekira Pak (paritaprevir, ritonavir, ombitasvir, +/- dasabuvir)	AbbVie	NS3/4A protease inhibitor; NS5A inhibitor; NS5B polymerase inhibitor	Marketed (US, EU, Japan, Brazil)
Zepatier (grazoprevir/elbasvir)	Merck	NS3/4A protease inhibitor; NS5A inhibitor	Marketed (US, EU)
Key Pipeline DAA Combinations With Furthest Achieved Clinical Stage			
Glecaprevir, pibrentasvir	AbbVie	NS3/4A protease inhibitor; NS5A inhibitor	Phase III (US, EU)
Daclatasvir, asunaprevir, beclabuvir	BMS	NS5A inhibitor, NS3/4A inhibitor; NS5B non-nucleoside polymerase inhibitor	Phase III (Japan)
Sofosbuvir, velpatasvir, GS-9857	Gilead	NS5B nucleotide polymerase inhibitor; NS3/4A inhibitor; NS5A inhibitor	Phase III (US, EU)
Odalasvir, AL-335, simeprevir	Janssen	NS3/4A protease inhibitor, NS5A inhibitor, nucleotide-based NS5B polymerase inhibitor	Phase II (US, EU)
Grazoprevir, MK-3682, MK-8408	Merck	NS3/4A protease inhibitor, NS5A inhibitor, nucleotide analogue NS5B inhibitor	Phase II (US, EU)

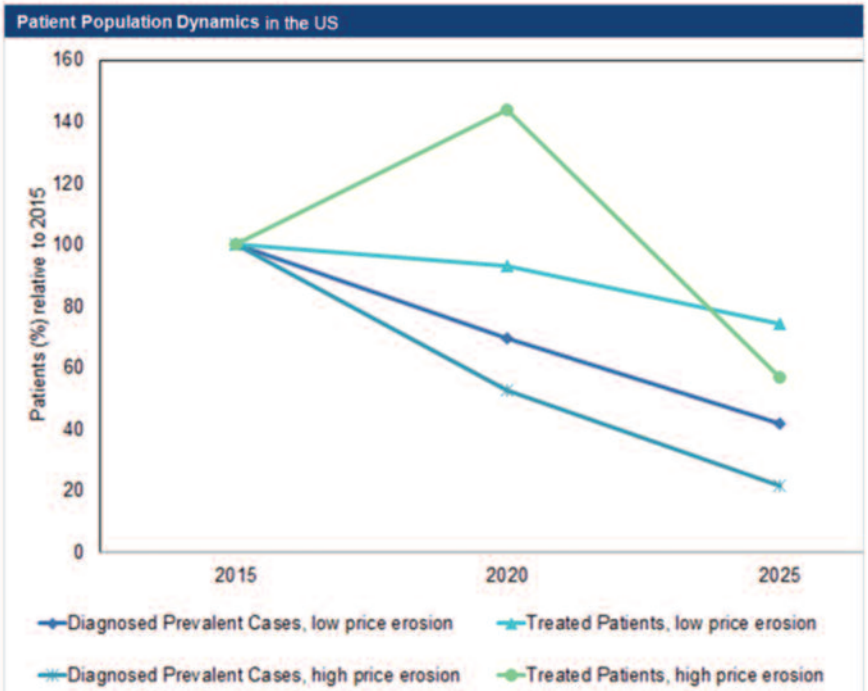
Source: GlobalData, Pipeline Products Pharma eTrack, October 2016.

CHANGES IN THE DAA TREATMENT LANDSCAPE

Fortunately, 2016 has ushered in a new phase in the treatment of hepatitis C. The launch of Gilead's Epclusa (sofosbuvir/velpatasvir) in July 2016 in the US was only the first in a row of pan-genotypic treatment alternatives. These new DAAs are not only expected to be recommended for all GTs, eliminating some of the treatment complexity, but also to provide significantly improved outcomes for patients currently considered as difficult to treat. In particular, patients with GT3, the second most prevalent GT in many European countries and third most prevalent in the US, will see significant improvements in their treatment outcomes as sustained viral response (SVR) rates are expected to reach similar levels as for GT1. Furthermore, the availability of multiple pan-genotypic combinations launching in the next few years can increase the number of treatment algorithms to avoid DDIs.

However, given the strong clinical profiles of current and future DAA regimens, companies need to develop alternative approaches to distinguish their brands from the competition. Although price is an important factor in this equation (see below), cost will not be the only determining factor in market success in the future, as companies will have strong incentives to keep the overall prices high for the next decade. An appealing approach chosen by several drug developers is the attempt to shorten

FIGURE 1



Source: GlobalData. Patient dynamics under two different scenarios. First scenario is limited price erosion and second scenario represents outcome under increased price erosion resulting in increased treatment rates. All numbers are standardized to 100% at 2015.

treatment durations. The time required for curing patients of chronic HCV has already been reduced from nearly 1 year about a decade ago to 12 to 24 weeks today, depending on the patient's GT and liver status. Harvoni already demonstrated high efficacy after 8 weeks of treatment in patients with GT1 and no cirrhosis, and both Gilead and Janssen are currently developing possible pan-genotypic DAAs that might be able to cure the same patient population after only 6 weeks of treatment.

Further possibilities in increasing market share in the future will lie in a further simplification of the treatment algorithm, for example by leveraging pan-genotypic treatments, improved efficacy outcomes for difficult-to-treat patients, and further improvements in safety/tolerability. Consequently, several clinical trials are currently assessing the efficacy of various DAAs in patients with severe comorbidities, including kidney and renal failure. Another possibly successful path for increased market penetration of a newly launching DAA is the complete elimination of ribavirin for patients with decompensated liver cirrhosis, a drug with possibly severe AEs.

FINANCIAL BURDEN OF TREATMENTS

Despite the clinical success of DAAs, the manufacturers are under heavy scrutiny by the public and politicians for the pricing policies of these life-saving treatments. However, while Sovaldi's wholesale acquisition cost (WAC) is listed for $84,000 and Harvoni's at $94,500 for a 12-week treatment, the average revenue per treatment reported by Gilead in 2015, including both 12- and 24-week-long treatments, was estimated to be around $54,000 and during the first 6 months of 2016 the price per treatment dropped another 22% — a possible response to the launch of Merck's Zepatier in January of 2016, listed at $54,000 per treatment. Clearly, most insurers in the US were able to obtain significant discounts for Gilead's HCV drugs, and corresponding price discounts are estimated for DAAs from other companies. Although the list price can exceed $1,000 per single pill, seen in context, the price is not necessarily high, as some cancer drugs can be priced beyond tenfold higher for a life-saving treatment algorithm. Furthermore, the simplicity of current HCV treatments, with a single pill taken once daily, absent of peginterferon injections or even stays in the hospital, might have contributed to the perception of HCV drugs being overpriced.

Nevertheless, despite these steep discounts, and the overall cost-effectiveness of many DAA algorithms, the treatment of hepatitis C represents a significant cost burden for most healthcare systems. Total sales for DAAs reached $22.7 billion in the 9MM in 2015, driven by the large number of patients requiring treatment, as the prevalence rate of HCV exceeds 1% of the overall population in several countries of the 9MM. As a response, many private insurances and nationalized healthcare providers have limited access to these drugs to rein in the overall cost of hepatitis C treatments, in particular for individuals not suffering from liver cirrhosis. However, several factors are driving the market toward more inclusive national treatment approaches. In the past 3 years alone, over 1 million people have been treated with Sovaldi-based regimens. Since most of these people will have been cleared of the virus, the total prevalence in most of the 9MM is now slowly decreasing. With fewer patients seeking treatment, healthcare providers can expand the medical cri-

teria for treatment initiation, for example from cirrhotic patients to patients with F3 or F4 fibrotic liver statuses. Other countries use an alternative approach. For example, France recently announced that, starting September of 2016, every patient with HCV will be permitted to receive reimbursed DAA treatment. However, the country also limits the annual expenditure at €0.7 billion per year, effectively allowing only less than 10% of the total prevalent cases to be treated in 2017. Simultaneously, countries also demand DAA manufacturers to cover the patient's treatment costs if the virus is not cleared after the completed treatment algorithm, an approach that, if successful, could also be implemented outside the HCV field.

With newly launching pan-genotypic drugs, the competitive landscape in the 9MM will further diversify and intensify in the upcoming years. The price erosion experienced during the past 2 years, however, is unlikely to continue, as overall HCV market dynamics are inclined against significant price reductions in the next years. Each of the five pharmaceutical giants with a pipeline product expected to launch during the next years already has a marketed product in most of the 9MM. Therefore, newly launching pan-genotypic drugs will likely be priced at a premium relative to existing DAAs. Furthermore, none of the currently marketed DAAs will lose patent protection during the next decade, preventing price erosion driven by the launch of generic products. However, the main reason for price stability can be found in the disease prevalence itself. Given the already high treatment rates in many countries, combined with low incidence rates and remarkably high SVR rates achieved by current DAA treatments, the patient population seeking treatment is decreasing. Particularly in the countries in which the pharmaceutical industry experiences the highest revenues, the US and Japan, the decline in diagnosed prevalent cases of chronic hepatitis C threatens the sustainability of future HCV drug revenues. Should the price erosion continue at a similar pace, the revenue stream could dry up many years prior to patent expiration. Another example of limited price erosion in the next year can be expected in France with an annual cap of €0.7 billion per year. Here, the country pre-defined the market size, and price erosion would translate into more patients being treated by each company's DAA regimen without translating into higher revenues.

GLOBAL OUTLOOK

The treatment of chronic HCV has undergone a seismic shift during the past few years and HCV can now be considered a curable disease in most patient populations. This success story also translates into higher barriers for companies, as intense competition limits market access while simultaneously the population pool targeted by these drugs is expected to decline in the next decade.

Despite the clinical success, several unmet needs remain in the market, with the overall cost burden of DAA treatments representing the biggest issues for the next years. Nevertheless, should governments initiate aggressive screenings to identify patients with HCV who have not been diagnosed in the past, in combination with broad application of DAA treatments even for non-cirrhotic patients, the overall burden of the disease could quickly fade. Although complete eradication across the 9MM during the next decade will be near impossible, a large initial investment into diagnostic screenings and treatment could translate into significant health-cost savings in the succeeding years, as declining prevalent cases not only result in fewer patients seeking treatment in the future but also lower the number of new infections and reduce associated healthcare costs related to liver cirrhosis, liver transplants, kidney failure, or liver cancer. As an alternative, healthcare providers might just wait on such an initiative until the launch of highly efficacious generic DAAs. ◆

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BIOGRAPHY

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NSCLC MARKET

Global Drug Forecast & Market Analysis to 2025

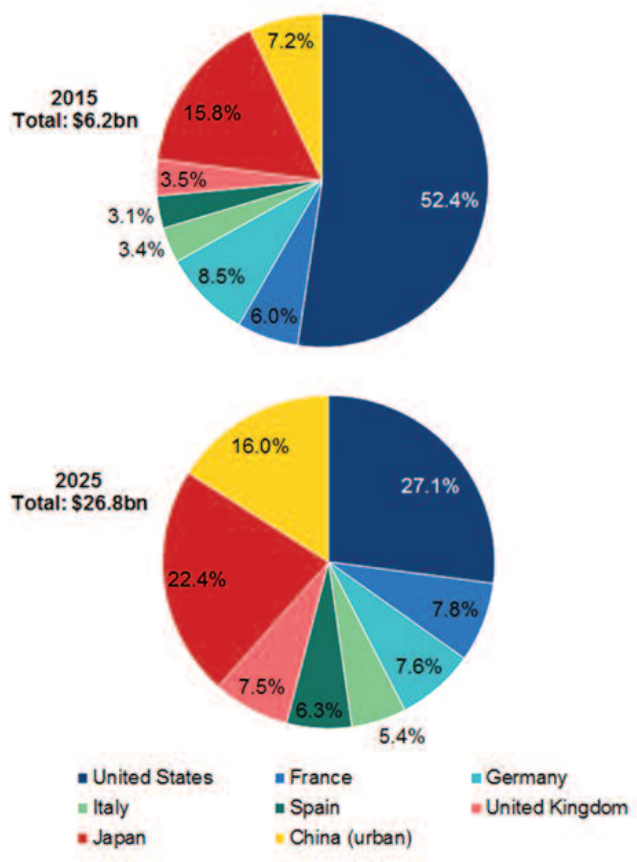
By: Cai Xuan, PhD, and Volkan Gunduz, PhD, GlobalData's Analysts covering Oncology

INTRODUCTION

GlobalData estimates that the value of the Non-Small Cell Lung Cancer (NSCLC) market in the 8 major markets (8MM) in 2015 was $6.21B. This market is defined as sales of major branded drugs commonly prescribed for NSCLC patients across the 8MM. Just over half of these sales, $3.25B (52%), were generated in the US, with the 5EU representing the next largest region by sales, estimated at $1.53B (25%). Japan and China contributed the smallest proportions of sales to the global NSCLC market, with 2015 sales of $981M (16%) and $445M (7%), respectively.

By the end of the forecast period in 2025, GlobalData projects NSCLC sales to rise to $26.8B in the 8MM, at a moderate Compound Annual Growth Rate (CAGR) of 15.7%. In particular, GlobalData expects the China NSCLC market to grow most rapidly, increasing to $4.3B (16% of global NSCLC shares) by 2025 at a robust CAGR of 25.4%. Sales in the other regions are also expected to increase by the end of the forecast period; however, the proportion of sales from the US and Japan are forecast to decrease to 26.9% and 22.3%, respectively, with market share in the 5EU increasing from 24.2% in 2015 to 34.3% by 2025.

FIGURE 1



Sales for NSCLC by region. (Source: GlobalData)

MAJOR DRIVERS OF GROWTH

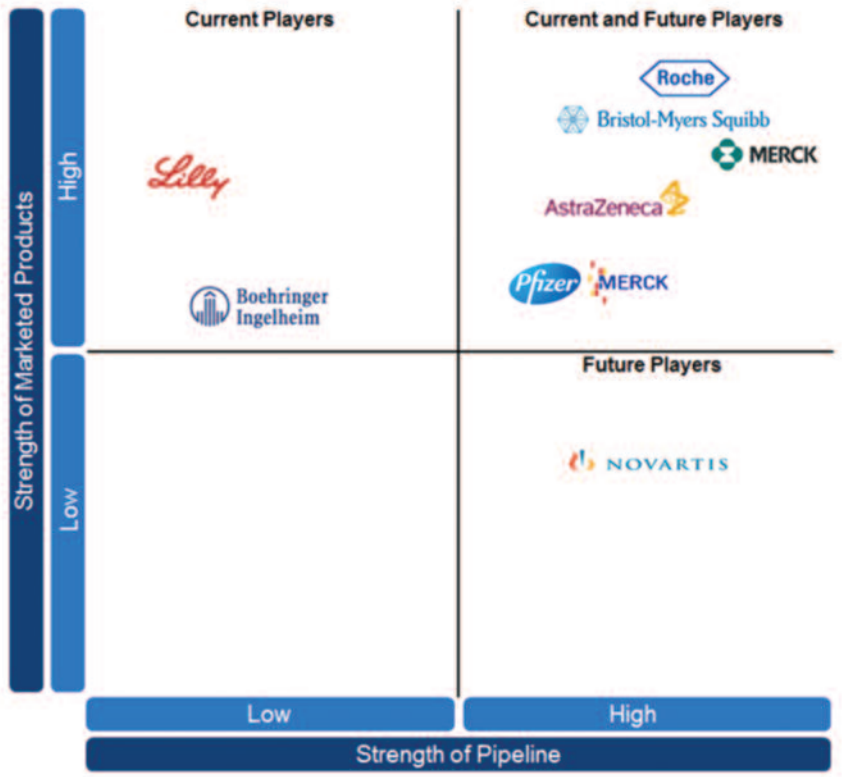
The increasing incorporation of premium-priced immune checkpoint inhibitor immunotherapies into the NSCLC treatment algorithm, particularly in the first-line setting, will be one major driver. Merck & Co.'s Keytruda (pembrolizumab), Bristol-Myers Squibb's (BMS') Opdivo (nivolumab), and Roche's Tecentriq (atezolizumab), will all achieve blockbuster status by the end of the forecast period. Collectively, immunotherapies will reach $17.5B in sales by 2025, accounting for roughly 65% of total sales in the NSCLC market. Of the $17.5B total, Keytruda, Opdivo, and Tecentriq are projected to contribute $5.2B, $5.5B, and $2.8B, respectively.

Targeted therapies are also expected to contribute to the growth of the NSCLC market. Overall, targeted therapies will have sales of $9.4B by 2025, with AstraZeneca's Tagrisso (os-

imertinib) and Roche's Avastin (bevacizumab) having the highest sales of this drug class, followed by Eli Lilly's Cyramza (ramucirumab). Tagrisso is projected to achieve blockbuster status by 2025, with $1.7B in estimated sales, reflecting a CAGR of 56.6% over the forecast period. Its sales will be driven by its uptake in the second line and, eventually, in the first-line setting in EGFR-mutant patients. Avastin sales are expected to grow modestly from $1.3B in 2015 to $1.6B by 2025 at a CAGR of 1.9%, fueled by increased uptake in nonsquamous patients, but stunted by biosimilar erosion that will occur in the 8MM over the forecast period, starting in 2018. In fact, Avastin's market share is sufficiently large that biosimilar bevacizumab is expected to achieve $1B in sales by 2025, assuming it will be priced at a 30% discount compared to branded Avastin. Cyramza sales are expected to grow from $84M in 2015 to $613M in 2025 at a CAGR of 22%, driven by launches in Japan and China.

The increasing incidence of NSCLC in the 8MM will also drive growth. China, in particular, will see its NSCLC incident cases increase significantly over the forecast period, at an Annual Growth Rate (AGR) of 4.7%. Overall, across the 8MM, the incidence of NSCLC is expected to increase at an AGR of 3.1% from 2015-2025. Growth in incidence is forecast to be most pronounced in urban China, where GlobalData expects there to be approximately 500,000 in 2025, rising from just over 330,000 cases in 2015 at an AGR of 4.7%. This increase, coupled with an anticipated increase in branded therapy prescriptions in China, will drive the growth of both the Chinese and global NSCLC markets over the forecast period.

FIGURE 2



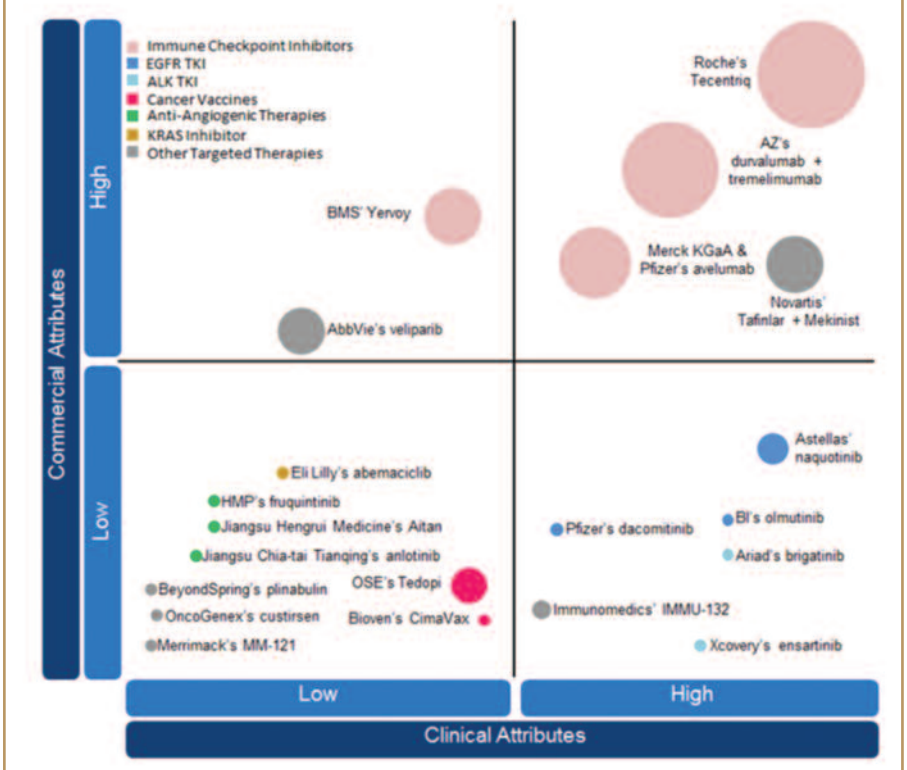
Company portfolio gap analysis in NSCLC. (Source: GlobalData)

MAJOR BARRIERS OF GROWTH

Patent expiration of several blockbuster drugs, including Tarceva and Alimta, will limit growth. Tarceva, the leading epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) in the NSCLC market, is expected to face patent expiry starting in 2016. GlobalData expects sales of the patented drug in the 8MM to decrease from $783M in 2015 to $18M by 2025. Meanwhile, sales of generic erlotinib are expected to reach $77M by 2025. In addition, sales of Alimta, which is commonly used in combination with chemotherapy in nonsquamous patients, will decrease from $2.1B in 2015 to $54M in 2025. Sales of generic pemetrexed are expected to reach $266M by 2025. GlobalData anticipates the uptake of generics to negatively impact the growth of the NSCLC market throughout the forecast period.

Pricing and reimbursement difficulties encountered by premium-priced drugs, especially in the European and Asian markets, are another major barrier. Increasing cost-consciousness will limit premium pricing opportunities for pipeline agents in the NSCLC market. Healthcare austerity measures are being incorporated across the major markets, and drug companies will need to consider the changing reimbursement landscape when determining pricing strategies for their drugs. GlobalData expects that this era of austerity and healthcare reform will negatively affect pharmaceutical companies' ability to gain reimbursement approval for their new NSCLC therapies, particularly immuno-oncology (IO) combinations that are extremely expensive.

FIGURE 3



Competitive assessment of late-stage pipeline agents in NSCLC. (Source: GlobalData)

COMBINATION THERAPY IS THE MAIN STRATEGY

In 2015, the NSCLC market was largely dominated by generic chemotherapy and targeted therapies, including EGFR and anaplastic lymphoma kinase (ALK)-TKIs, accounting for approximately 94% of the NSCLC market, while IO sales accounted for just 6%. In 2025, that trend will be reversed, with 65% of the total NSCLC market going to IO therapies, and the remaining 35% being split between chemotherapy and targeted agents.

A major trend in corporate strategy is the pairing of programmed cell death protein 1 (PD-1) checkpoint inhibitors with other agents. In the crowded PD-1 space, as drugs with identical mechanisms of action (MOAs) are launched, companies are looking for ways to boost efficacy in hopes of differentiating their product from that of their competitors. As such, companies like Merck & Co., Roche, and BMS are evaluating their PD-1 checkpoint inhibitors in combination with chemotherapies, targeted agents, and/or other IO products. BMS has high hopes for the combination of Opdivo + Yervoy (ipilimumab) in first-line therapy, while Merck & Co. and Roche have focused on evaluating IO + chemotherapy combinations. Roche is also investigating the combination of its programmed death ligand 1 (PD-L1) inhibitor Tecentriq + chemotherapy + Avastin in chemotherapy-naïve nonsquamous NSCLC patients in the ongoing Phase III IMpower 150 trial.

Currently, BMS is the market leader in the second-line setting, with Merck & Co. coming in second due to the inconvenience of Keytruda's label restriction hampering its uptake. This ranking is not expected to change during the forecast period, as Opdivo has a stronghold in the second-line setting. However, in the first-line setting, due to Keytruda's anticipated first-to-market advantage as a monotherapy in PD-L1+ patients following Opdivo's Phase III failure, GlobalData expects Merck & Co. to become the market leader over the forecast period. Roche also has a strong pipeline strategy, evaluating combinations of Tecentriq with chemotherapies and/or targeted therapies in multiple Phase III trials that all have the potential to lead to approval.

A FOCUS ON IMPROVING TARGETED THERAPY OPTIONS

In the targeted therapy arena, companies are developing novel therapies for previously unactionable mutations. KRAS mutants are an example of a patient subpopulation that makes up a significant (25% to 30%) share of the total NSCLC patient pool, but for which there are no targeted therapies currently available. Eli Lilly & Co.'s pipeline agent abemaciclib targets KRAS patients, yet its lack of efficacy is expected to severely limit its uptake, leaving opportunities for other KRAS targeted therapies to enter the space. Recently, AstraZeneca's selumetinib, another KRAS targeted therapy, failed its Phase III trial, leaving the KRAS mutant population without any effective late-stage pipeline drugs. In addition to KRAS, BRAFV600E is also being explored as a target. This mutation has already been successfully targeted in melanoma by the combination of Novartis' Tafinlar (dabrafenib) + Mekinist (trametinib), which is expected to make a big impact for this patient population. However, the size of the eligible patient pool will limit its sales to $318M for Tafinlar and $278M

for Mekinist by 2025.

In addition to novel therapies, companies are also developing second- and third-generation targeted therapies to provide better options for patients with actionable mutations. These newer targeted therapies commonly overcome resistance from first-generation treatments, and/or have superior efficacy in certain subpopulations. For example, AstraZeneca's Tagrisso is effective in Tarceva/Iressa (erlotinib/gefitinib)-resistant EGFR mutation positive (EGFRm+) patients, while Roche's Alecensa (alectinib) and Novartis' Zykadia (ceritinib) have both been reported to be effective in ALK mutation positive (ALKm+) patients with brain metastases. GlobalData expects these next-generation targeted therapies to take significant patient share away from their predecessors. Tagrisso is expected to achieve sales of $1.7B by 2025, while Alecensa and Zykadia are expected to achieve sales of $600M and $127M, respectively. All three drugs will have high CAGRs, with Tagrisso being the highest, at 56.6%, followed by Alecensa at 24.5%, and Zykadia at 13.3%. The sales of EGFR-TKIs as a class will grow at a CAGR of 4.9%, while the ALK-TKI sales will grow at a CAGR of 10.7%. Targeted therapies other than EGFR- and ALK-TKIs are also expected to see significant sales growth, from $1.5B in 2015 to $5.3B by 2025.

UNMET NEED IN THE NSCLC MARKET EXPECTED TO DECLINE

One of the main unmet needs in NSCLC treatment is the need for more effective first-line treatment options that provide overall survival (OS) benefits to patients with no actionable mutations. Currently, the standard-of-care in the first line is platinum-doublet chemotherapy, which has significant systemic toxicity and low compliance rates. During the forecast period, PD-1 checkpoint inhibitors are expected to launch in the first-line setting both as monotherapies and in combination with chemotherapy or CTLA4 checkpoint inhibitors. With the entry of these IO products, first-line treatment algorithms are expected to change, with IO drugs expected to take a majority of patient share away from standard chemotherapies.

REMAINING UNMET NEED IS HIGHEST WHERE?

Although the current and future IO drugs will significantly reduce unmet needs in NSCLC, there remains high unmet need in the PD-L1-negative patient population. This population of patients has been shown to receive minimal benefit from PD-1 agents thus far. There has been some evidence that the combinations of IO + IO or IO + chemotherapy, such as Opdivo + Yervoy and Keytruda + chemotherapy, respectively, may enhance response rates in this patient pool, but the data are preliminary and need to be confirmed in larger patient populations in ongoing clinical trials.

OPPORTUNITY REMAINS

An opportunity remains for drugs that target novel biomarkers/mutations in NSCLC. KRAS mutants, which account for a significant portion (25% to 30%) of the total NSCLC patient population, are the most underserved patient segment, with no currently available targeted drugs. Further, there are also rare mutations that lack targeted therapies. For example, NSCLC patients with the BRAFV600E mutation, which has already been success-

TABLE 1

2015 Epidemiology	
Incident Population	791,563
Total Population	1.99M
2015 Market Sales	
US	$3.3B
5EU	$1.5B
Japan	$981M
China (urban)	$445M
Total (8MM)	**$6.2B**
Pipeline Assessment	
Number of drugs in Phase III	21
Number of first-in-class drugs	9
Most Promising Pipeline Drugs	**Peak-Year Sales**
Atezolizumab (Roche, Tecentriq)	$2.8B
Avelumab (Merck KGaA)	$754M
Durvalumab + tremelimumab (AstraZeneca)	$1.3B & $929M
Key Events (2015–2025)	**Level of Impact**
Keytruda launch in first-line PD-L1+ NSCLC	↑↑↑
Alimta patent expiry	↓↓↓
Keytruda + Platinum-Alimta launch in first-line nonsquamous NSCLC	↑↑↑
Tagrisso launch in first-line EGFR-mutant NSCLC	↑↑↑
Tarceva patent expiry	↓↓↓
2025 Market Sales	
US	$7.2B
5EU	$9.2B
Japan	$6.0B
China	$4.3B
Total (8MM)	**$26.8B**

Source: GlobalData; primary research interviews and surveys conducted with KOLs and high-prescribing physicians in the 5EU countries.

The key metrics for non-small cell lung cancer (NSCLC) in the eight major pharmaceutical markets (8MM) — the US, five major European markets (5EU: France, Germany, Italy, Spain, and the UK), Japan, and China — during the forecast period from 2015-2025.

fully targeted in melanoma, have no available targeted therapies at this stage. During the forecast period, the unmet need for drugs targeting novel biomarkers/mutations will decline with the entry of the first-in-class, KRAS-targeting pipeline drug, Eli Lilly's abemaciclib. For BRAFV600E-mutant NSCLC, Novartis' combination therapy of Tafinlar + Mekinist, which is already approved to treat BRAFV600E+ melanoma, is expected to become available.

Despite the launch of drugs addressing the unmet need in KRAS and BRAFV600E patients during the forecast period, there remains opportunity for further development of targeted therapies, particularly in squamous NSCLC. Since the mutations found in squamous NSCLC are almost entirely distinct from well-described mutations, such as EGFR and ALK that occur in nonsquamous disease, there is ample opportunity for companies to develop targeted therapies against mutations associated with squamous NSCLC. Some of these include PIK3CA amplification/mutation, FGFR1, PTEN, and DDR2.

IMMUNO-ONCOLOGY DRUGS: RAPID UPTAKE

Roche's Tecentriq is expected to launch in combination with chemotherapy and/or Avastin in the first-line setting for NSCLC. It is a "me-too" drug that will compete with marketed products Opdivo and Keytruda, both of which are already approved in the second line and are seeking label expansions into the first line. Projected peak-year sales for Tecentriq are $2.8B. The majority of these sales will come from the first line, but a small portion will also come from the second-line setting once Tecentriq gains approval.

AstraZeneca's combination of durvalumab + tremelimumab is expected to launch in the first- and third-line settings in NSCLC. This combination is one of two that pair a PD-1 inhibitor with a CTLA4 inhibitor — the other being Opdivo + Yervoy. Projected peak-year sales for durvalumab and tremelimumab are $1.7B and $1.1B, respectively. Durvalumab + tremelimumab combination therapy is expected to lag behind monotherapy and IO + chemotherapy combinations in uptake due to its high cost.

WHAT DO THE PHYSICIANS BELIEVE?

IO drugs are generating excitement within the NSCLC community, as they provide a much-needed alternative to chemotherapy in the second-line setting, especially for squamous NSCLC patients. However, despite the enthusiasm for, and expected rapid uptake of, IO drugs during the forecast period, some KOLs have mixed views on PD-1 checkpoint inhibitor use in NSCLC. They view the low response rates seen with PD-1/PD-L1 inhibitor therapy and the high costs of these drugs as negatives, and speculate that their widespread use in all patients would be financially impractical. GlobalData expects that these concerns will need to be addressed in the form of combination therapies that increase response rates and potentially elicit responses in PD-L1-negative patients; with regard to cost, concerns can be addressed through pricing negotiations between companies and national healthcare agencies in order to support the widespread use of IO drugs in NSCLC. Alternatively, IO drugs may eventually be restricted to patients with the highest expression levels of tumor PD-L1 as a way for payers and nationalized healthcare systems to control costs in the long run. ◆

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BIOGRAPHIES

Dr. Cai Xuan is an Oncology Analyst at GlobalData in Boston. She provides in-depth scientific analysis of products within the oncology pharmaceutical sector and constructs market forecast models based on business intelligence. She has authored several expert insights that delve into market analysis of innovative treatment strategies in oncology. She earned her BS and PhD in Microbiology, Immunology, and Molecular Genetics, from the University of California, Los Angeles (UCLA). Prior to joining GlobalData, she was a post-doctoral fellow at the John Wayne Cancer Institute in Santa Monica, California.

Dr. Volkan Gunduz is an Oncology Analyst at GlobalData in Boston. He offers in-depth market intelligence and data interpretation within the oncology pharmaceuticals sector. He earned his PhD in Genetics at Tufts University, where he studied the role of Retinoblastoma tumor suppressor protein in bone development and cancer. He earned his BSc in Molecular Biology and Genetics at Bilkent University, Turkey. Previous to joining GlobalData, he worked at Children's Hospital Boston and New York University as a post-doctoral fellow working on projects that investigated the impact of dietary restriction on lung tumorigenesis and the gene network that regulates muscle stem cell identity.

PLATFORM TECHNOLOGY

The 3DNA® Platform for Targeted Drug Delivery

By: Robert C. Getts, PhD, and Jessica Bowers

INTRODUCTION

Nanotechnology and targeted delivery have emerged as unique strategies for improving therapeutic efficacy while minimizing toxicity and off-target effects. Targeted nanocarriers can be used to deliver novel drug candidates and to provide new formulations of matured therapeutics. Multivalent-engineered nanostructures also hold the possibility to deliver combination therapeutics.[1-3] There are several nanotech-based drugs already launched and hundreds of new targeted treatments under development.

Genisphere's 3DNA® joins the list of targeted drug delivery nanoreagents, including by broad definition, liposomes, quantum dots, gold nanoshells, micelles, magnetic nanoparticles, dendrimers, and carbon nanotubes. While a variety of polymeric materials are used to manufacture these nanocarriers, Genisphere's 3DNA nanotechnology platform is DNA-based and is composed of a cross-linked network of uniquely designed DNA strands.[4] Looking to expertise in both Pharma and Academia, Genisphere has been leveraging a collaborative model to advance several drug delivery programs, and is also progressing its own lead compounds based on the 3DNA platform.

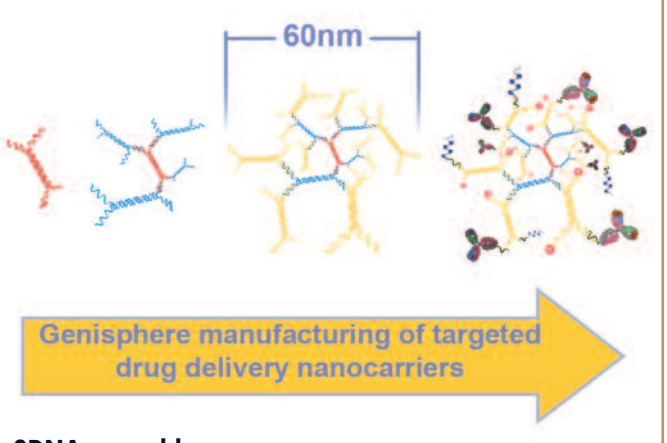
3DNA ASSEMBLY

Genisphere routinely manufactures therapeutic quantities of drug delivery nanocarriers called 3DNA. The manufacturing process is intended to consider the need for nanocarriers with a truly modular design. Like other nanoreagents, 3DNA is constructed using materials, in this case, DNA, that are not new to the FDA.

Specifically, Genisphere uses seven unique sequences of single-stranded DNA designed to hybridize to one another to create building block monomers, each with a central double-stranded region and four terminal single-stranded regions (Figure 1). By design, it is possible to manufacture five unique monomers. The monomers themselves hybridize to each other in specific orientations, due to base-pairing between complementary single-stranded regions. For assembly, monomers are hybridized and crosslinked to each other in a step-wise fashion of forming layers (Figure 1), and a two-layer core 3DNA nanoscaffold with a diameter of 60 nm is typically used for drug delivery applications. Importantly, crosslinking during manufacturing ensures the stability of the core 3DNA structure, providing a shield from the harsh physiological environments often found in vivo.

Genisphere has functionalized 3DNA with a variety of targeting devices and drug cargoes, depending on the intended use. Therapeutics successfully conjugated to 3DNA include small molecules, proteins, peptides, miRNA, siRNA, mRNA, and plasmid DNA. Typical targeting devices are selected based on an up-regulated marker on the cell of interest, and include antibodies, antibody fragments, peptides, sugars, vitamins, and other targeting devices. Like other nanocarriers, 3DNA uses targeting devices to ensure specificity and minimize off-target drug effects. Similarly, sustained-release formulations are possible to manufacture, by modulating attachment chemistry, using PEG or other stealth molecules, or incorporating into a hydrogel formulation.

FIGURE 1



3DNA assembly

WHY DNA?

DNA as a nanotechnology matrix offers a unique set of physical, chemical, and biological properties.[5,6] Because 3DNA is completely and only made of DNA, it is soluble, biocompatible, and biodegradable into non-toxic material, with a metabolic clearance pathway already known to the host organism. Given its unique properties, structural flexibility and solubility, 3DNA is not really a nanoparticle, but rather a nanocarrier. Using DNA offers versatility in assembly and control of the physical size or shape of the nanocarrier. 3DNA is uniformly negatively charged, and is designed with a base composition to avoid activation of the immune response typically characterized by cytokine production and up-regulation. Biodistribution, accumulation at desired site, and clearance are only determined by 3DNA targeting moieties, not by the core structure.

3DNA has hundreds of drug attachment sites that can allow lower doses to achieve the same efficacy as free drug when the appropriate targeting moiety is selected. In addition, 3DNA is completely customizable for targeting or multi-targeting with two or more unique moieties per single nanocarrier. This flexibility in multivalency enables delivery of a targeted combination therapeutic to, for example, engage the immune system while delivering a cytotoxin to disease cells. Because there are many options for conjugating DNA to drugs, 3DNA enables delivery of a broad range of drug compounds. Multiple linker chemistries can be used in the same construct, enabling differential drug release. Importantly, two or more different drugs may be coupled to the same 3DNA molecule, in both the core and also on the periphery, further maximizing the therapeutic payload.

3DNA CHARACTERISTICS

Safety

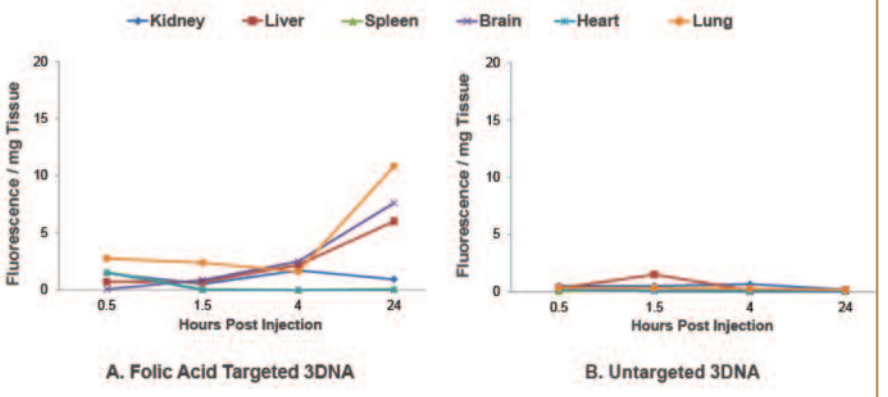
In mouse and rabbit models, no toxicity has been observed at therapeutic dose levels or after chronic treatment of various 3DNA formulations. Throughout the course of these studies, all animals appeared healthy, demonstrated normal behavior, and showed no signs of toxic effects nor change in body weight due to the administration of the 3DNA nanocarrier. Immunocompetent mice demonstrated little to no cytokine activation 0.5-48 hours after systemic administration of 3DNA nanocarriers. Both deep sequencing and PCR have been used to show 3DNA nanoscaffolds are degraded after cargo delivery in vivo, with no impact/integration to target cell genome.

Biodistribution

To study biodistribution using radiolabeled antibodies, mice were injected with either radiolabelled anti-ICAM antibody, or a 3DNA targeted against the same radiolabelled anti-ICAM antibody. The animals were sacrificed, organs were excised, and isotope was counted and compared to determine the presence of control antibody versus targeted 3DNA. Interestingly, only the liver showed similar distribution between the two delivery systems, while kidney, brain, spleen, heart, and lung showed higher presence of 3DNA, suggesting 3DNA did not accumulate in the liver like other nanoparticles. Of particular note was the 3DNA crossing the blood-brain barrier in mice.

In another simple biodistribution study (Figure 2), folic acid-targeted, Cy3-labeled 3DNA was compared to untargeted Cy3-labed 3DNA (no drug cargo was used). Various organs were collected immediately prior to sacrificing the mice at specific time points post injection. Samples from non-injected animals showed minimal levels of auto-fluorescence and no nanostructure-like fluorescence, as expected. Untargeted 3DNA nanocarriers did not accumulate in tissues, while targeted 3DNA nanocarriers accumulated only in tissues expressing the folate receptor. Specifically, 3DNA nanocarriers with folic acid attached as the targeting molecule bound to specific cells in the brain, liver, and lung within 4-24 hours following injection.

FIGURE 2

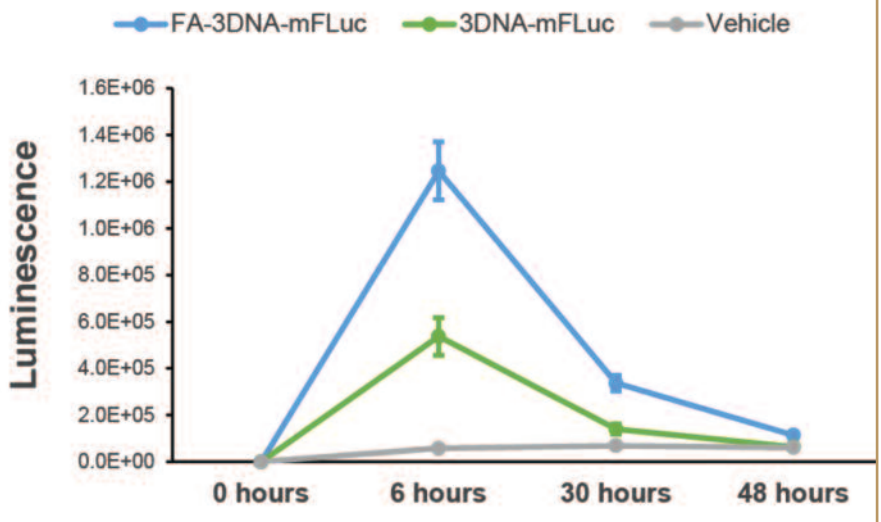


3DNA biodistribution

Targeted Delivery of Payload

Genisphere pursued a collaboration with Dr. Janet Sawicki at the Lankenau Institute for Medical Research to demonstrate functional in vivo delivery of a cargo molecule. Specifically, commercially available luciferase mRNA was combined with a specially designed 3DNA containing folate as a targeting molecule (FA-3DNA-mRNA). The 3DNA was designed to bind the mRNA via a sequence within the mRNA itself. As a control, untargeted 3DNA with luciferase mRNA (3DNA-mRNA) was also prepared. Each of the formulations as well as vehicle were intraperitoneally injected into mice bearing orthotopic ovarian tumors. At various time points, the animals were imaged for bioluminescence to determine the relative luciferase expression over time (Figure 3). Based on the imaging results, the ovarian tumors were the only observable targeted tissue, maximal mRNA expression occurred 6 hours after injection, and targeting was required for efficient delivery. Untargeted 3DNA demonstrated minimal luciferase expression, further supporting the requirement for targeting and the overall lack of an EPR dominant effect.

FIGURE 3



Time course of firefly luciferase expression using folic acid targeted 3DNA delivery

APPLICATION IN OPHTHALMOLOGY

Cataract surgery is one of the most common procedures performed throughout the world, but it is not without complications. While surgery restores vision in the majority of cases, up to 40% of adults and most children develop a secondary cataract, a vision-impairing condition called posterior capsule opacification (PCO). Laser treatment is required to correct PCO, but it is expensive and can be risky. Genisphere's therapeutic candidate GL-249 has been designed as a quick and easy treatment to prevent PCO at the time of cataract surgery, by immunodepleting the cells that cause PCO.

The specific cells in the eye that contract and produce wrinkles leading to PCO can be targeted by a unique monoclonal antibody. This antibody is used as a targeting device on 3DNA loaded with doxorubicin, a cytotoxic drug, and the resulting GL-249 formulation has been studied in mouse and rabbit models. Rabbits aggressively develop PCO 4 weeks after cataract surgery, and in one study, GL-249 reduced the incidence of the condition in rabbits compared to controls when delivered at the time of cataract surgery.[7] Further development of sustained-release formulations may lead to a quick and easy method to prevent PCO at the time of cataract surgery, and open the door to treating other serious conditions of the eye.

APPLICATION IN ONCOLOGY

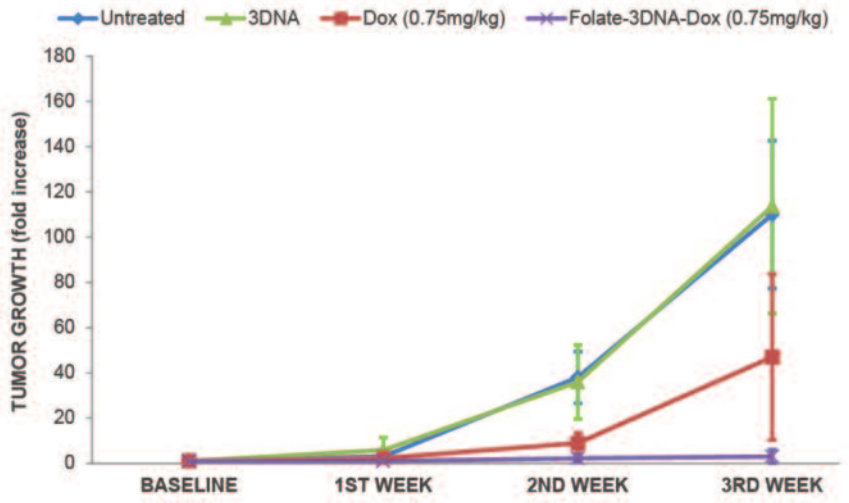
In a preliminary study, ovarian tumor-bearing mice were injected with untargeted Cy3-labeled 3DNA or with Cy3-labeled 3DNA with either folic acid, anti-transferrin receptor antibody, or anti-folate receptor antibody-targeting moieties. The animals were sacrificed, and various tissue sections were prepared and viewed to confirm the expected biodistribution of targeted 3DNA. The targeted Cy3-3DNA was observed in the center area of the tumor, with little staining in the stroma, while untargeted Cy3-labelled 3DNA did not localize to the tumor. To assess if the various targeted Cy3-labeled 3DNA were directed to the tumor via macrophage uptake, ovarian tumor sections were labeled with F4/80 antibody to detect macrophages. Macrophage staining was observed in cells in the stroma and adipose tissue (when present), and a few single cells in the tumor demonstrated little co-localization with the Cy3-labeled (3DNA targeted) tumor cells. Because no dual-labeling was observed, it is believed

the presence of targeted, Cy3-labeled 3DNA observed in the tumors is not due to macrophage uptake and is a result of true targeting.

To test delivery of a small drug molecule, mice bearing ovarian tumors derived from ID8-Fluc bioluminescing cells were systemically injected twice a week for 3 weeks. The injected formulations included the cytotoxin doxorubicin, delivered as free drug or delivered using folate-targeted 3DNA. At the end of the short study, it was observed doxorubicin delivered with folate-targeted 3DNA significantly hindered ovarian tumor growth compared to the same dose of free doxorubicin (Figure 4).

A similar mouse ovarian tumor model was used in a study using folate-targeted 3DNA formulations to deliver siRNA (lead candidate GL-233).[8] Human antigen R (HuR), also called ELAVL1, is an RNA-binding protein that regulates the expression of genes known to function in tumor cell survival and in drug resistance. A double-stranded siRNA to HuR was designed with modified RNA bases for stability, and an extension of 23 ribonucleotides on the 3′ end of the passenger strand for hybridization to single-stranded peripheral portions of 3DNA. In this case, mice bearing ovarian tumors derived from ID8-Fluc bioluminescing cells were intraperitoneally injected twice a week for 4 weeks. Both tumor growth and ascites development were reduced in animals treated with 3DNA reagents compared to control formulations. A follow-up study (Figure 5) of the folate-targeted siHuR 3DNA (GL-233) showed extended survival of mice treated with GL-233 (49 days) compared to control animals (31 days). GL-233 is being investigated as a complementary approach to current, active therapies for ovarian cancer for overcoming drug resistance and inhibiting tumor growth.

FIGURE 4

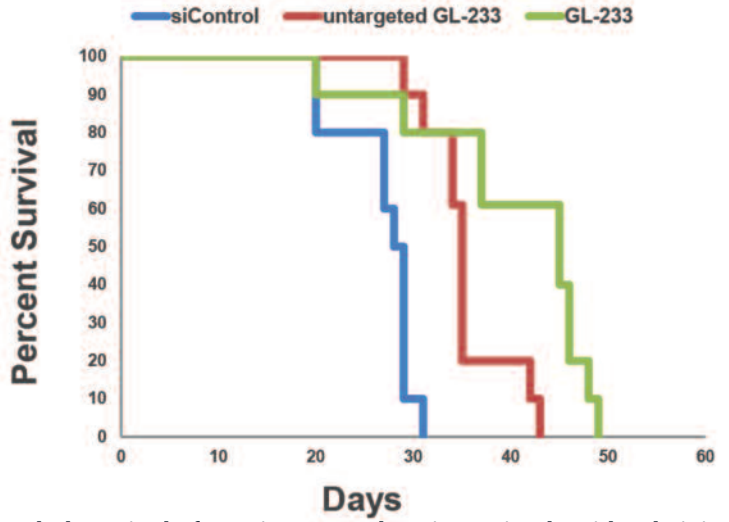


Inhibition of ovarian tumor growth using folate-targeted 3DNA to deliver doxorubicin

SUMMARY & FUTURE DIRECTIONS

Genisphere's 3DNA platform is composed entirely of noncoding DNA assembled through the sequential hybridization of single strands of DNA into a network of double-stranded nucleic acid having a controlled architecture, and multiple attachment sites for drug and targeting molecules. The flexibility of the 3DNA platform enables targeted delivery applications in gene delivery, biologics, small molecules, and RNAi therapeutics. Through collaboration and on its own accord, Genisphere has advanced several 3DNA-based lead compounds, and seeks additional partnerships for development of clinically relevant programs. For example, Genisphere recently announced a collaborative research agreement with the University of Pennsylvania for photodynamic therapy (PDT), in which 3DNA specifically targeted to breast cancer cells will be used

FIGURE 5



Extended survival of ovarian tumor-bearing animals with administration of GL-233

to deliver photosensitizing drug. PDT is a complementary treatment option for early stage cancer. After tumor tissue is surgically removed, photosensitizing drugs are administered and activated by visible light to destroy any remaining cancerous cells. The delivery of PDT to the entire surgical field is essential, thus selective photosensitizer accumulation in diseased cells is necessary to avoid therapy-limiting damage to normal tissues. On the industrial side, Genisphere recently publicized a research and option to license agreement with MedImmune, the global biologics research and development arm of AstraZeneca. The partners will develop 3DNA nanocarriers using up to six of MedImmune's oncology molecules.

Genisphere continues to explore utility of 3DNA in versatile applications. Future areas of interest include CRISPR gene-editing strategies for oncology and neurotherapeutics based on multi-targeted 3DNA nanostructures. With the emergence of new translational tools in medicine and the growing need for individualized care for patients, the 3DNA platform provides just the right amount of flexibility to rapidly adapt to patient needs while maintaining high therapeutic efficacy and little to no toxicity, ultimately enabling both individualized care and combination therapy. ◆

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BIOGRAPHIES

Robert C. Getts, PhD, is the Vice President of Research and Development and CSO at Genisphere. Since joining the company 22 years ago as a Senior Research Scientist, he has actively developed outside relationships with project collaborators and potential partners in the biotech research and business communities for work on original and custom products and technologies. He has led the development of Genisphere's 3DNA nanotechnology and IP portfolio as a signal amplification platform for improving sensitivity in life science and diagnostic assays (for microRNA and mRNA) and more recently as a pre-clinically validated targeted delivery platform for cancer, cardiovascular, and central nervous system indications. Dr. Getts has over 25 publications to his credit and continues to publish peer-reviewed manuscripts and review articles. He has more than 15 issued patents domestically and internationally and more than 35 submitted patent applications internationally. In recent years, Dr. Getts has been focused on drug discovery and the pre-clinical development of Genisphere's 3DNA platform for both Genisphere and partner pharmaceutical company Lead candidates, leading to the development of an extensive dataset in support of this work.

Jessica Bowers is the Marketing Director at Genisphere. Since joining the company in 2002, she has supported product launches, provided technical and sales support to a global base of customers, and guided corporate communications. She serves as project coordinator for Genisphere's collaborations with academic institutions for targeted drug delivery.

PROTEIN THERAPEUTICS MARKET

Technology Advances Spur Market Growth of Protein Therapies

By: Laurie L. Sullivan and Shalini S. Dewan, Analysts at BCC Research

INTRODUCTION

With the advent of genetic engineering and recombinant DNA technology, it is now possible to produce a wide variety of human proteins. BCC Research found that these novel technologies have lifted the market for therapeutic proteins to new heights. Recombinant DNA technology has created an ease in the manufacturing of protein therapeutics and is replacing traditional natural methods of extraction. The rising demand for high-quality recombinant therapeutics is motivating the research and development of mammalian cell–based manufacturing systems for improved production yields.

Indeed, protein therapeutics have become an important segment of the healthcare industry, and their numbers have increased in recent years. With their many advantages over small-molecule drugs, protein therapies form a promising market; they are less likely to interfere with normal biological processes, and they are often well tolerated. Because of their high specificity and low immunogenicity, protein therapeutics are widely used to treat various diseases such as cancer, diabetes, and multiple sclerosis.

In terms of revenue, monoclonal antibodies are the largest market segment. The increased incidence of many chronic diseases has driven use of monoclonal antibodies. However, this segment faces competition from the entry of follow-on biologics. Vaccines are another growth segment in the biopharmaceutical industry. The improving economic conditions, increasing public awareness of vaccination, and global efforts of governments to eradicate viral and bacterial infections are key drivers. Improved manufacturing technologies have also fueled the vaccines market.

Improvements in technologies such as mass spectrometry, advances in molecular genetics, and progress in production technologies are all key drivers of the protein therapeutics market. In addition, rapid advances in medical technologies, improved diagnosis of diseases, and the expansion of healthcare in emerging markets should have a positive impact on the market. Patent expiries and increasing competition are also major influences.

The global market for protein drugs reached $174.7 billion in 2015. At a 5-year compound annual growth rate (CAGR) of 7.3%, it is predicted to attain $248.7 billion by 2020. By region, the United States is the largest market, valued at nearly $92 billion in 2015. The United States is also the fastest-growing, and with a projected 5-year CAGR of 10.9%, the revenue for this region is forecast to be $154.1 billion by 2020. Europe, which reached $42.2 billion in 2015, is expected to total $48.1 billion by 2020, reflecting a 5-year CAGR of 2.6%.

The market for protein drugs is analyzed broadly according to the following types: peptide hormones, monoclonal antibodies, cytokines, therapeutic enzymes, blood factors, vaccines, and peptide antibiotics.

TABLE 1

Global Revenue for Protein Drugs by Region Through 2020 ($Millions, Source: BCC Research)

Region	2013	2014	2015	2020	CAGR% 2015-2020
United States	74,775.30	81,303.50	91,990.00	154,087.80	10.9
Europe	41,448.90	44,875.30	42,202.00	48,068.50	2.6
Emerging Markets	38,904.00	41,132.40	40,487.20	46,496.60	2.8
Totals	**155,128.20**	**167,311.20**	**174,679.20**	**248,652.90**	**7.3**

Peptide Hormones

Peptide hormones include human growth hormones, insulin, erythropoietin, and gonadotropins. Hormonal disorders are on the rise due to the increase in obesity and decreased physical activity. The introduction of delivery systems and devices for the convenience of consumers has also boosted the peptide hormones market. The insulin market is expected to grow in the coming years due to the increasing diabetic population. And gonadotropins are used for treatment of infertility disorders, which are expected to rise commensurately as the childbearing age increases.

The peptide hormone market is principally divided into growth hormones and erythropoietin. Human growth hormones have gained importance as therapeutic agents; however, generic versions of some products are already available. Widespread renal anemia has increased the demand for erythropoietin, making it a major contributor to the peptide hormone market. Darbepoetin, a second-generation erythropoietin, allows patients to administer doses less frequently; therefore, the market share of darbepoetin is rising.

The global market for peptide hormones reached $30.4 billion by the end of 2015, bolstered by new drug approvals. A dip in the erythropoietin segment was in part due to increased competition; the introduction of less-expensive biosimilars is expected to push the market in a downward direction. The human growth hormone market remained almost stagnant in 2015; due to the availability of generic drugs, it is not expected to grow much.

Vaccines

In terms of generating revenues, vaccines are one of the brighter spots for manufacturers. The increasing acceptance of adult vaccines, public awareness of flu prevention, and introduction of new vaccines are key growth factors. Various government programs and increased public awareness of bacterial diseases such as meningitis, diphtheria, and typhoid have augmented vaccination rates in various countries. The vaccines market is driven by population growth and the need for therapeutic vaccines for cirrhosis, liver disease, and primary liver cancer.

The vaccines market is characterized by moderate growth prospects, higher capital investments, and increased inputs in research and development activities. With novel manufacturing technologies (for example, the use of embryonated eggs for influenza vaccines), the time and cost required to manufacture vaccines are reduced. The World Health Organization has predicted that widening access to vaccines could prevent 24.6 million to 25.8 million deaths by the end of the decade.

The overall vaccines market is forecast to grow well due to innovations and discoveries for newer vaccines against diseases such as malaria. Viral vaccines represent the largest segment, driven by the wide spread of diseases such as influenza and hepatitis. The viral vaccine market has benefitted from governmental awareness programs for diseases such as polio and measles. There has been significant growth in the bacterial vaccine market, worth $12.8 billion in 2015. This segment is expected to continuously grow at a CAGR of 10.9% to 2020.

Therapeutic Enzymes

Therapeutic enzymes are used to treat enzyme deficiencies, which can lead to various types of metabolic and enzymatic disorders. Some enzymatic disorders require enzyme replacement therapy, in which the specific enzyme that is inactive or absent in affected individuals is replaced with a functional enzyme molecule that is isolated or produced in a lab. En-

zyme therapy is used for cystic fibrosis, pancreatic insufficiency, and certain cancers.

The global therapeutic enzyme market is divided into lysosomal enzymes, pancreatic enzymes, and others (mainly thrombolytic enzymes). Increasing sales of branded products are primarily driving growth of the overall enzymes market. The global market for therapeutic enzymes, dominated by the lysosomal segment, reached $6.6 billion in 2015 and is expected grow at a CAGR of 10.4% to 2020.

Monoclonal Antibodies

The commercial achievements attributed to monoclonal antibodies in the last few years are incomparable to any other therapeutic class. Driving forces for the monoclonal antibodies market include the increasing incidence of cancer; the specific advantages of monoclonal antibodies as therapeutic agents; higher demand to address unmet therapeutic needs in immunology and oncology; and lower competition as the result of accessing novel target space. A broad-spectrum mode of action is another remarkable advantage of monoclonal antibodies, making them useful in various diseases. Because of their high specificity, monoclonal antibodies have become very important as targeted therapies.

The market scenario for monoclonal antibodies is changing due to launches of biosimilars. The patents of most monoclonal antibodies are set to expire before 2020. The first biosimilar molecule, which is an infliximab biosimilar, will be joined by eight others by 2020. The series of launches, however, may not immediately shake the branded antibody market. The complex structure of monoclonal antibodies, a long and complicated manufacturing process, and stringent regulatory requirements will restrict entry of a large number of biosimilars to the market. The market for human monoclonal antibodies is anticipated to increase at a CAGR of 16.6% to 2020.

Cytokines

The cytokines market is broadly characterized as colony stimulating factors, interleukins, and interferons. The deciding factors for this market have been the launch of hepatitis B and C cytokine therapies, as well as immunity boosting cytokine therapies. The latter are used during and after organ transplantations, and to fight infections during chemotherapy. The global cytokines market is growing moderately. The increasing number of patients with hepatitis and the price increases of therapeutic interferons are the driving forces. The availability of biosimilars in European and other countries is a restricting factor for the cytokines market.

Interferons led the cytokines market with $7.1 billion in 2015, followed by granulocyte colony stimulating factors. The interleukin segment will experience the most growth through 2020, driven by an aging population across all regions and subsequent increase in incidence of age-related macular degeneration.

Blood Factors

Blood factors are a major contributor to the protein therapeutic industry. More use of blood factors is required as the incidence of bleeding disorders increases. The aging population is another growth factor because older people are prone to developing diseases with higher demand for blood derivatives.

The blood factors market is principally divided into coagulation factors (the predominant segment) and immunoglobulins. Recombinant versions of various coagulation factors are the major drivers for growth of this segment. The global immunoglobulin market is also growing well, due to continuous demand for immunoglobulin treatments as well as the approval of existing intravenous immunoglobulin products for new indications.

The blood factors market is dominated by sales of coagulation factors, which reached $10.5 billion in 2015 and will likely increase during the next few years. Products derived through recombinant technology are less contaminated than those derived through the process of natural extraction, and thus are more acceptable to manufacturers and consumers. Factors driving the immunoglobulin market include sales of existing products, increased diagnoses, and a rise in prophylactic treatment of immune diseases.

Peptide Antibiotics

Peptide antibiotics (including cyclosporine, vancomycin, bacitracin, and others) are relatively small molecules. They act quickly and lethally against a broad spectrum of pathogens and escape many of the drug-resistance mechanisms. Recent advances in organ preservation and procurement techniques have contributed to an increasing number of organ transplants and the development of new peptide antibiotics.

In 2015, cyclosporine was the strongest segment of the peptide antibiotic market, worth nearly $1.9 billion. The emergence of antibiotic-resistant bacteria has caused a decline in the use of vancomycin, which is facing the availability of alternative or new treatment options for in-

vasive methicillin-resistant Staphylococcus aureus infections. The peptide antibiotics market has also been negatively affected by the onset of generics. However, this market is expected to rebound as the result of new approvals in recent years, and to increase through 2020.

FACTORS AFFECTING THE PROTEIN THERAPEUTIC MARKET

It is expected that the increase in the aging population and attendant age-related diseases will inevitably lead to growth in the protein therapeutic market. Chronic conditions such as diabetes, cancer, autoimmune disorders, and cardiovascular diseases are becoming more prevalent. According to the World Health Organization, chronic diseases will become the seventh-leading cause of death worldwide by 2030. By virtue of their higher efficacy and fewer adverse effects, protein therapeutics are helpful in treating such diseases. Thus, the increase in persons suffering from these diseases has led to growth in the protein therapeutic market.

Advancements in manufacturing technologies are another major factor in the protein therapeutic industry. Traditionally, proteins were extracted from human or other biologic resources. For example, vaccines were made using egg cultures. However, with the advent of recombinant DNA technology, manufacturers can now produce large quantities of vaccines using genetically modified organisms. Blood products were initially extracted from human plasma; however, they are now manufactured using DNA technology, either in bacterial expression systems or in mammalian cell culture systems. Growth in the protein therapeutic market is likely to mirror these advances in manufacturing technologies.

The high cost of protein therapeutics is a major challenge. High product prices result in the unavailability of certain therapies that are required by patients for quick and effective recovery. At the same time, prices are controlled by law in many countries. Government agencies regulate prices through their control of national healthcare organizations, which can bear a large part of the cost for supplying medicines to consumers. European governments are adopting aggressive pricing strategies to exert downward pressure on drug costs. Healthcare reforms in countries such as France, Spain, and Germany have controlled pricing and authorized generics. In the United States, there are no government price controls over private sector purchases, but federal law requires manufacturers to pay rebates on certain medicines to be eligible for reimbursement under several state and federal healthcare programs.

The healthcare and medical industries are highly regulated. Regional/country-specific laws and regulations are important determinants of whether a product can be successfully developed and approved. The benefit-to-risk evaluation continues to be a chief consideration in the approval of new medicines, and regulatory authorities are increasingly focusing on the safety of medications during the post-approval phase. Every country governs its own laws of regulation, making it harder for manufacturers to meet the requirements for each. Therefore, regulatory pressures create a challenge in the market for protein therapeutics.

Finally, the availability of biosimilars in European and other countries is a restricting factor for the protein therapeutics market. Many top-selling drugs are approaching patent expiry, paving the way for biosimilars. In March 2015, the US FDA approved the first biosimilar in the United States, Zarxio, for filgrastim. Thus, the North American market scenario is expected to change with the onset of biosimilars. ◆

This article is based on the following market analysis report published by BCC Research: Global Markets and Manufacturing Technologies for Protein Drugs (BIO021E) by Shalini Shahani Dewan. For more information, visit www.bccresearch.com.

To view this issue and all back issues online, please visit www.drug-dev.com.

BIOGRAPHIES

Shalini S. Dewan earned her MS in Pharmaceutical Chemistry and has more than 14 years of industry experience. She was awarded a Gold Medal by the Prime Minister of India for her work and has worked with top companies in India and in the US. Some of her other reports for BCC Research include: Global Markets and Technologies for Advanced Drug Delivery Systems, Orthopedic Drugs, Implants and Devices and Global Markets for Reagents for Chromatography.

Laurie L. Sullivan, ELS, is a Boston-based writer and editor with 20 years of experience in medical communications. She is certified by the Board of Editors in the Life Sciences. She contributes regularly to the BCC Research blog focusing on Life Sciences.

DNA SEQUENCING MARKET

Emerging Technologies & Applications

By: Laurie L. Sullivan and John Bergin, MS, MBA, Analysts at BCC Research

INTRODUCTION

Since its commercial introduction more than a decade ago, next-generation sequencing (NGS) has matured into an essential life science tool for genetic studies in a range of applications. BCC Research recently reported that the NGS industry is on the cusp of a second growth phase, powered by new applications in clinical diagnostics.

The worldwide market for sequencing products is forecast to grow at a 5-year compound annual growth rate (CAGR) of 18.7% to reach nearly $13.8 billion by 2020. The market can be segmented into pre- and post-sequencing products (ie, sample preparation reagents/kits and informatics, respectively), sequencing instruments and consumables, and sequencing services.

Sequencing services is the largest and fastest-growing segment, with an anticipated 5-year CAGR of 26%. BCC Research forecasts the value of the sequencing services segment to exceed $9 billion by 2020. The high growth rate is due to a number of factors, including the expansion of sequencing into new applications in the clinical and applied market segments.

The main clinical applications driving market growth are cancer and reproductive health. The other main clinical sequencing applications through 2020 include Mendelian disorders, infectious diseases, and complex disorders.

Cancer Applications

The main cancer applications for NGS diagnostics include tumor sequencing, familial screening, monitoring for cancer recurrence, and liquid biopsy. Cancer diagnostics that provide the genetic profile of a tumor can have an influence on which therapy is chosen. This is a critical driving force behind NGS-based tumor sequencing diagnostics. The key issue for this application is establishing a clinical connection between a given tumor mutation profile and an effective therapy. It is believed, however, that many large-scale sequencing projects are addressing this issue and that significant progress is being made.

Current applications for NGS in cancer are focused on discrete sets of genes. However, BCC Research believes that whole exome and whole genome sequencing will gain traction in the future as sequencing costs fall and the value of testing for only a

TABLE 1

Global Sequencing Market by Product Type, 2014-2020 ($Millions, Source: BCC Research)

Product Type	2014	2015	2020	CAGR% 2015-2020
Sequencing instruments, reagents & consumables	2,778.00	2,981.30	4,686.50	9.5
Sequencing services	2,527.20	2,869.80	9,122.50	26
Total	**5,305.20**	**5,851.10**	**13,809.0**	**18.7**

single gene or several genes declines. Longer term, it is expected that most tumors will be completely sequenced, giving physicians full genetic information for treating their patients.

The second application for cancer is familial screening of relatives of patients with cancer and those who may otherwise be at high risk. The key driving force for this application is a reduction in sequencing costs to the point where there are significant cost-benefit advantages for NGS tests. A second driving force in familial screening is breakout into the general population. There is evidence that many people who have no family history of cancer can carry risk mutations. Because most people at risk will not undergo NGS-based screening tests without insurance reimbursement, costs must continue to decrease and clinical validity must be established.

Monitoring is a key application for liquid biopsy formats. Monitoring during the course of treatment is desirable because it can assess tumor growth, metastases, or resistance to therapy. Monitoring during therapy also allows physicians to make adjustments based on the changing genetic profile of the tumor. For cancer monitoring, the early commercial tests are gene-specific quantitative tests. However, the industry is evolving toward multigene panels that cover clinically actionable mutations in a range of genes and cancer types.

Monitoring post-treatment focuses on finding minimal residual disease or cancer relapse. Liquid biopsies for monitoring recurrence are designed to detect low levels of tumor mutation and to measure tumor mutation quantities over time to assess cancer recurrence. More than 95% of all cancer deaths worldwide happen after relapse. Finally, NGS-based tests that can help choose appropriate patients to enroll in clinical trials, as well as once a new drug enters the market, will help in the selection of treatment based on a patient's genetic profile.

Mendelian Disorders Applications

NGS diagnostics are used for difficult-to-diagnose rare genetic diseases, with multiple tests on the market. The key driving force for this application is deficiencies in conventional approaches. Diagnostic odysseys occur when an individual has a rare genetic disorder and undergoes many expensive and invasive clinical tests and procedures to determine the cause. These cases frequently occur in clinics that evaluate children for such things as cognitive impairment, neuromuscular disorders, or congenital anomalies.

Diagnostic odysseys often include serial molecular testing of one or a few genes, running up the costs of diagnosis. Many of these rare genetic diseases are due to a single-gene mutation in the genome. They are referred to as Mendelian disorders because they comport with the inheritance pattern first discovered by Gregor Mendel.

BCC Research believes there are as many as 25 million individuals in the US who have inherited Mendelian disorders. Some of these are well understood, including cystic fibrosis and muscular dystrophy, but others are much rarer. There are approximately 6,000 of these very rare disorders, and only half of them have been identified. NGS is changing the diagnostic paradigm in these cases because it can rapidly and more cost-effectively deliver a correct diagnosis than conventional approaches.

The key advantage of NGS is that it is highly multiplexed to cover many genes in one test format, including genes for which no commercial molecular test exists. One of the key challenges to implementing NGS for this application is demonstrating to the medical community the clinical value of such test formats. BCC Research believes that this challenge is being aggressively addressed by a number of leading institutions in this field, as well as by several high-profile initiatives.

Reproductive Health Applications

The non-invasive prenatal screening (NIPT) market has been a major success story in the industry. The main clinical benefit of the non-invasive test format is a reduction in the number of unnecessary invasive procedures, which in turn results in less risk of resultant miscarriage. A secondary clinical benefit is an earlier diagnosis of fetal aneuploidy. NIPT is experiencing a high adoption rate among women at high risk of having babies with chromosomal abnormalities.

Since the introduction of initial tests, providers have sought to expand their testing menus. This is a key strategy to getting higher market share in the at-risk population. A key issue that will impact the future market potential is whether or not NIPT will be adopted by the average-risk patient population. For this to happen, insurance providers and other payor groups will need to recognize a clear clinical benefit to screening this population segment.

For newborn screening, NGS offers much promise, assuming that it continues down the cost curve. The key driving force for this application is the decline in costs of sequencing and associated informatics. For commercial success, it is critical to demonstrate that NGS tests can provide more relevant clinical genetic information at a price point lower than that of the current methods. If this can be done over the

"The worldwide market for sequencing products is forecast to grow at a 5-year compound annual growth rate (CAGR) of 18.7% to reach nearly $13.8 billion by 2020. The market can be segmented into pre- and post-sequencing products (ie, sample preparation reagents/kits and informatics, respectively), sequencing instruments and consumables, and sequencing services. Sequencing services is the largest and fastest-growing segment, with an anticipated 5-year CAGR of 26%. BCC Research forecasts the value of the sequencing services segment to exceed $9 billion by 2020. The high growth rate is due to a number of factors, including the expansion of sequencing into new applications in the clinical and applied market segments."

next few years, it is likely that insurance companies will come onboard, and a viable market will result.

There are ethical issues associated with NIPT and newborn screening, many of which will be resolved over time as the tests mature and there is greater experience among the screening population and physicians. For many disorders, the phenotype is hard to predict, and as a result, it may not correlate with sequencing data. This would limit the ability of the physician to make informed decisions based on a sequencing test.

There is also the problem of trying to implement a set of informed consent and genetic counseling guidelines for non-invasive testing. This is particularly true for broad-based sequencing tests, for which there are many variants of unknown significance that make interpretation difficult. A final issue is the potential impact of NIPT tests on abortions. These ethical issues have not prevented the high growth of NGS-based tests for prenatal screening. BCC Research views the ethical issues as interesting to consider, but they have little impact on the market for these tests.

NGS is newly emerging for preimplantation screening, driven by the increased success rates of in vitro fertilization applications. A main hurdle is offering these tests at an attractive price point versus microarray methods, and thereby increasing the penetration of NGS. The tests do not rely on insurance coverage because they are offered with direct payment from the patient. This feature has attracted the interest of a significant number of companies. Both NGS and microarray-based tests evaluate chromosomal aneuploidy, with screening for single-gene disorders also emerging for these tests.

Infectious Disease Applications

The main applications of NGS diagnostics for infectious diseases include outbreak tracking and human immunodeficiency virus (HIV) tropism. In outbreak tracking, the use of NGS to diagnose patients who are hospitalized with foodborne infections is viewed as a near-term point of entry. A positive development for this application is the use of MiSeq in regional laboratories throughout the US to track foodborne pathogens and outbreaks. This is being done under a pilot program sponsored by the FDA.

A main obstacle to commercialization will be the education of clinicians regarding the benefits of using NGS tools to quickly identify pathogen strains so that effective treatments can be implemented. Because the initial application will be for hospitalized patients, it will be important for developers to market the new tests appropriately to critical care physicians and to contrast the benefits of NGS with older methods. NGS must compete with both polymerase chain reaction (PCR) and Sanger sequencing to meaningfully penetrate the infectious disease market.

One application in which NGS has shown near-term commercial promise is HIV tropism testing. The genotypic assay uses Sanger sequencing, which is the gold standard for HIV tropism testing. However, NGS provides a better detection limit, such that mutations at lower allele frequencies can be detected. These lower-frequency

mutations may be important in predicting drug resistance. It is thought that frequencies as low as 1% may influence drug sensitivity, and the present limit of Sanger sequencing is 20% frequency.

Complex Disorders Applications

Complex disorders applications include immune system disorders, metabolic/mitochondrial disorders, cardiovascular diseases, and neurological diseases. Genetic factors may play only a minor role in some diseases, limiting the impact of NGS as a diagnostic. For other diseases, genetics may well play an important role. It is likely that as new knowledge is gained regarding the genetic basis for these diseases, the need for NGS diagnostics will increase.

For immune system disorders, the main applications include immune system profiling, human leukocyte antigen (HLA) typing, rheumatoid arthritis (RA), and multiple sclerosis (MS). In the field of immune system profiling, NGS is making progress through commercial assays and research. Although Sanger sequencing is the current standard of care for high-resolution HLA typing, NGS assays provide rapid, high-resolution typing at a competitive cost. Research into the genetic underpinnings of RA and MS is ongoing, and NGS technologies are useful tools in this effort. As this research progresses, it is expected that new molecular diagnostics will be developed, some of which will use NGS formats.

Mitochondrial disorders are difficult to diagnose because they have complex genetic causes and a wide range of phenotypes, making these diseases well suited for NGS diagnostics. For this market segment, single-gene tests do not provide enough information, and whole exome sequencing is too costly and overkill. For metabolic/mitochondrial disorders, a key driving force is deficiencies in conventional approaches.

Cardiovascular and neurological disorders comprise a strong potential future market for NGS diagnostics. NGS tools have been used to show that breakdown in the control of gene expression may help to initiate or progress some of these diseases. The market for NGS diagnostics will come to fruition when clinical research can correlate genetic changes with the risk of disease onset or progression.

CLINICAL SEQUENCING TECHNOLOGY CHALLENGES

Many challenges must be overcome for NGS to be widely adopted in the clinical setting. Sequencing costs must continue to decline at the rate predicted by Moore's law. Price points are bringing NGS into broader competition with other molecular diagnostic technologies, such as PCR, microarrays, and lab-on-a-chip. Insurance coverage must continue to expand for NGS-based tests. There is evidence of increasing coverage by payors in some key NGS clinical markets, including NIPT and cancer.

Genetic testing generates data specific to each patient, and there are social and ethical concerns about the means to secure the privacy of these data, as well as who can access it. These questions will become more important as the clinical test market grows and as more complex tests, including those based on whole genome sequencing, are introduced.

Informatics is a key technical challenge for NGS diagnostics. For NGS data to be clinically actionable, it must be analyzed, correctly interpreted, and put into a simple report format for physician use. The time and resources required for handling and storing large amounts of genetic data remain a key bottleneck in the industry. Because of this, the informatics industry will be a critical factor in the future success of NGS diagnostics. ◆

This article is based on the following market analysis report published by BCC Research: DNA Sequencing: Emerging Technologies and Applications (BIO045F) by John Bergin. For more information, visit www.bccresearch.com.

To view this issue and all back issues online, please visit www.drug-dev.com.

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Drug Development
EXECUTIVE

Michael Graffeo
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Insulet Delivery Systems Group

Insulet Corporation

Insulet Corporation: Improving Adherence Through Wearable, Patient-Centric Drug Delivery

Patients have a choice. Insulet Corporation has an answer. With the increasing number of biologics and therapies available to patients today, pharmaceutical and biotechnology companies face a challenge in not only ensuring efficacious delivery of their drugs, but also that patients will select their drugs over the many other options available. This dynamic is creating a new future for subcutaneous delivery. Pharmaceutical and biotechnology companies are being driven to utilize patient-centric delivery devices that will fit volume requirements and ensure patient adherence. Insulet's Omnipod Insulin Management System has been improving the lives of patients with diabetes for over a decade, and this technology platform now is being used for improving drug delivery in other therapeutic areas. *Drug Development & Delivery* recently interviewed Michael Graffeo, Vice President of Business Development, Insulet Delivery Systems Group, to discuss the importance of optimizing patient adherence to ensure improved clinical outcomes.

Q: How does Insulet see the role of wearable devices in the future of the drug delivery market?

A:With an increasing number of injectable drugs and biologics coming to market, the route of administration is set to play an important role during drug development. More than 800 new highly viscous biologics are expected to come to market by 2025. These drugs require a device that allows for larger volume delivery over a prolonged injection period. That's where wearable devices offer a significant benefit over traditional needles or autoinjectors.
Across the global healthcare system, there is also an increasing focus on patient centricity – enabling patients greater freedom to live their lives without being restricted by their drug delivery regimen. Insulet is working toward technologies that provide better adherence, simplified delivery, and greater clinical efficiencies.
The least valuable drug is the one that's not taken — so any innovation needs to offer greater convenience, patient centricity, and therefore greater adherence. The Omnipod Delivery System platform is designed to help to address these issues.

Q: What benefits does Insulet bring to pharmaceutical and biotechnology companies seeking to improve patient adherence?

A: For more than a decade, Insulet has delivered intelligent, virtually pain-free subcutaneous administration for drugs with complex dosing regimens often restricted by conventional methods of injection. We have more than 85,000 patients worldwide who count on the Omnipod Insulin Management System – and we are the only wearable device manufacturer with that track record.
For pharmaceutical and biotechnology companies, this means we hear and understand patient needs, and we have developed a proven device that is liked by those who wear it, and backed by those who recommend it. We continue to increase the number of patients using the Omnipod technology and enjoy positive feedback from long-term patients.

Initially, the Omnipod System was designed to allow people living with diabetes to live their lives and manage their diabetes with unprecedented freedom, comfort, convenience, and ease. As the world's first commercially available tubeless insulin delivery system, Omnipod allows users to live untethered by tubing and without the stress and anxiety of multiple daily injections.

This same principle has now been applied to other therapeutic areas in which drug partners require innovative and patient-centric delivery options. For over 10 years, individuals with diabetes have been counting on Insulet to provide a safe and reliable drug delivery device. Pharmaceutical and biotechnology companies can have the same confidence in the design, delivery, and satisfaction of Omnipod delivery for a variety of therapies. In addition, the Omnipod platform is customizable depending on dosing profiles.

Q: What does the industry look for from companies like Insulet in regard to wearable technology?

A: The needs of the industry – from pharmaceutical companies to the patient – are multi-faceted. Safety and reliability are key components to any wearable technology – but offering a patient-centric device is also important to ensure optimal adherence.
Practically speaking, delivery devices need to be flexible to allow for commercially available drugs. This could mean providing a device that is prefilled for time of use, activated at the time of filling, and/or developing a continuous monitoring system to improve patient adherence. Consistency of delivery is also a key safety factor to ensure the device does not over or under deliver. Smart, wearable devices like Omnipod can include advances in technologies like Bluetooth/remote patient monitoring to help track patient adherence. Additionally, there are various dosing profile options offering data management insights that can help both patient and healthcare professionals better understand delivery and adherence information.

Q: What makes the Omnipod System patient centric?

A: To Insulet, it is about making the lives of patients and users easier so they can live life on their own terms with the ease of use they deserve. This means we ensure the method of delivery is convenient, simple, trustworthy, and allows patients to live a life free from self-injection. Patient centricity brings the freedom to live life at home, without having to regularly go back to the hospital or clinician.

In terms of development, it's about putting the patient at the center of all we do. Ultimately, if a patient isn't going to wear it,

"In terms of development, it's about putting the patient at the center of all we do. Ultimately, if a patient isn't going to wear it, creating a device that will fit as much volume as possible does not further adherence. We created our device with the patient in mind. When it comes to the Omnipod platform, we have created the only wearable, intelligent, subcutaneous delivery device commercially available."

creating a device that will fit as much volume as possible does not further adherence. We created our device with the patient in mind. When it comes to the Omnipod platform, we have created the only wearable, intelligent, subcutaneous delivery device commercially available.

The Omnipod platform has the ability to modify dosing and delivery times, as well as monitor patient adherence – making it a user-friendly and easy-to-use delivery system. Additionally, for non-insulin delivery, Omnipod has a remote-less option for pre-programmed dosing regimens. Its auto-cannula insertion means patients never have to handle the insertion needle. Omnipod is discreet, tubeless, and waterproof – reducing life interference and improving drug adherence.

Most importantly, we deliver the Omnipod Insulin Management System to more than 85,000 users worldwide. Their feedback enables us to make continuous improvements and deliver a device that strives to address those needs. These insights have been critical to the success of our business.

Q: Do you believe delivery time matters when a pain-free and patient- centric device is used?

A: For years, the industry has focused on devices that inject medication in 30 to 60 seconds. At Insulet, we believe that wearable technology changes the dynamic significantly. Current perceptions linking injection pain or difficulty and delivery time are based on older technology, such as autoinjectors or subcutaneous devices that require patients to hold them in place.

Moreover, studies have shown that patients have discontinued self-injection for reasons, including: fear and frequency of the injections, and reactions around the injection site. These ultimately make the injection experience uncomfortable and patient adherence low.

When it comes to innovative wearable technology, a device such as the Omnipod System offers virtually pain-free delivery, with users wearing the device for up to 3 days. As an industry, we need to better understand pain associated with delivery of different drug types in order to develop these more patient-centric and efficacious devices. Many of our Omnipod System users have moved from multiple daily self-injection with a syringe or autoinjector to wearing the Omnipod for up to 3 days. This push for faster delivery is no longer relevant in the future of drug delivery.

Q: What experience does Insulet have working with top 20 pharmaceutical companies?

A: Insulet has two existing commercial agreements and additional development agreements with multiple other pharmaceutical companies. Each project requires different modifications to be made to the delivery device, which we have the flexibility to do.

Q: How does Insulet approach its partnerships with pharmaceutical companies?

A: Our primary goal is to reduce the burden of injectable medicines on patients and improve outcomes through an increase in medication adherence. In order for this to be achieved, Insulet approaches each relationship with potential partners as a combined effort in which both Insulet and the partner company work in tandem to develop solutions that address patient needs and reasons for non-adherence. We consider ourselves to be committed to developing unique delivery solutions that patients prefer. Using our 15 years of commercial success in delivery drugs/therapeutics using our Omnipod technology platform and combining that with our partners' knowledge of disease challenges and drug development, we work together to tailor customized solutions to suit volume, formulation, delivery requirements, delivery administration, and patient needs. Fostering partnerships and strong relationships with pharmaceutical companies allows us to create a patient-centric device that can help provide better outcomes for both patients and partners.◆

Alcami is a world-class supplier of comprehensive pharmaceutical development and manufacturing services headquartered in Wilmington, NC. With nearly 1,000 employees operating at seven sites in the US and Europe, our combined capabilities include API development and manufacturing, solid state chemistry, formulation development, analytical development and testing services, clinical and commercial finished dosage form manufacturing (oral solid dose and parenteral), packaging, and stability services. We offer a world-class end-to-end outsourcing opportunity as well as individualized development and manufacturing services that can be integrated for a less fragmented and faster pathway for products through the clinical toward commercialization. With a flexible and responsive approach, you benefit from our highly integrated operations. Our expertise ensures the best possible outcome for your product at every level.

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BASF We create chemistry

BASF creates chemistry for a sustainable future offering intelligent solutions to the pharmaceutical industry. With our expertise in polymer chemistry, R&D-capabilities, and commitment to developing excipients, BASF creates solutions for Instant & Modified Release, Solubilization, Softgels, Skin Delivery, and Biologic applications. We also are a leading supplier of selected APIs, such as ibuprofen and omega-3. Our team of experienced industry specialists are here to support you in developing effective, reliable solutions to the formulation challenges you face today and tomorrow.

It is often the simple solution that sorts out a complex problem. At BASF, we know that innovation, speed-to-market, and cost-effectiveness are crucial to pharmaceutical companies. With expertise across the entire pharmaceutical value chain, we deliver on all three accounts, from lab to launch.

Equipped with an in-depth understanding of multiple industries, technologies, and applications, we have the skills and resources to make drug manufacturing more efficient, robust, and cost-effective. Whether you want to make your medicine more effective, safer, or more patient-friendly, we will help you find the solution to your formulation challenges.

Our **Instant & Modified** release solutions offer an unprecedented range of functionality, which means we can help you formulate pharmaceuticals with the exact release properties you desire. This ensures the precision you need every time.

Our **Skin Delivery** platform provides a portfolio of excipients spanning a wide range of solubility parameters for use in semi-solids, gels, liquids, and transdermal patches to increase drug penetration through the skin. What's more, our excipients are proven to be mild and non-irritating in highly sensitive clinical studies.

Our **Softgel** portfolio offers leading-edge functional excipients to help achieve the best possible results for each element of a softgel – whether coating, shell, or fill. Moreover, all ingredients have been tested according to the highest quality standards to minimize the possibility of crosslinking.

We offer a comprehensive range of cutting-edge **Solubilization** polymers, and have an unparalleled understanding of the corresponding process technologies. This unique combination means that we can make sure you achieve effective solubilization across a range of dosage forms – particularly in solid dispersions. And because we are a pioneer in the application of hot-melt extrusion technology in pharmaceutical production, we can help you combine effectiveness with cost efficiency.

Rely on us to help solve your drug development challenges.

BASF Corporation
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Florham Park, NJ 07932
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BioScreen® Testing Services
3904 Del Amo Blvd. No. 801
Torrance, CA 90503
T: (310) 214-0043 F: (310) 370-3642 W: www.bioscreen.com

BioScreen Testing Services is a full-service GMP contract laboratory specializing in Analytical Chemistry, Microbiology, and Stability services. All testing complies with ISO 9001:2008, cGMP, and can be performed GLP upon request.

Analytical Chemistry

BioScreen has over 30 years of analytical experience. We specialize in method development and validation for HPLC, GC, GC-MS, ICP, and ICP-MS. All validation packages are delivered to the client ready for FDA review or submission. Studies can be conducted GMP or GLP.

Pharmacopoeia Testing per USP, EP, BP, JP, FCC, ACS, AOAC, and other Monographs
Active Pharmaceutical Ingredient (API) - Drug Substance
Excipient
Bulk Release
Drug Product/Finished Product
Water Testing
Total Organic Carbon Determination, USP, EP (2.2.44)
Conductivity Measurement, USP
Heavy Metals Testing, USP
Elemental Impurities - Limits, USP
Elemental Impurities - Procedures, USP
Cleaning Validation Studies
Leachables & Extractables, USP, EP (3.2.2)
Residual Solvents, USP
Container Closure Integrity/Dye Immersion
Content Uniformity
Dissolution Testing, USP
Physical Testing

Stability

Long & Short-Term Stability
Drug Substance or Drug Product Stability
IND, NDA, ANDA, Stability
Photostability
Protocol Design for R&D Stability & Formulation Evaluations

Stability Storage

All ICH Conditions
Ultra Low Freezer at -84°C to -66°C
Freezer at -20°C to -10°C
Freezer at -25°C to -15°C
Refrigerated at 2°C to 8°C
Photostability Chamber
Custom Conditions Available Upon Request

Microbiology Services

BioScreen has 30 years of experience in microbiology testing for pharmaceutical, biotechnology, and other FDA-regulated industries.

Microbiological Examination of Nonsterile Products: MLT per USP and BP/EP, JP, US
Antimicrobial Effectiveness Tests: USP, EP, JP, ISO
Bacterial Endotoxin Tests: USP, BP/EP
- Gel Clot
- Kinetic
  - Chromogenic
  - Turbidimetric

Sterility Test: BP/EP, USP
- Direct Immersion
- Bacteriostasis/Fungistasis
- Membrane Filtration
  - Close (Steri Test)
  - Open

Particulate Matter: USP, BP/EP
- Light Obscuration
- Microscopic

Container Closure Study (Microbial Ingress)
Microbial Reconstitution Study
AMES Test (Mutagencity Test)
- OECD # 471

Susceptibility Tests
- Minimum Bactericidal Concentration (MBC)
- Log Reduction (Time Kill Study)

Heterotrophic Plate Count
Microorganism Identification
- Vitek
- Analytical Profile Index (API)

Strategize pathways for growth,
rejuvenate product innovation,
and allocate your resources
with reliable industry analysis.

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information@bccresearch.com

Capsugel®

Capsugel designs, develops and manufactures a wide range of innovative dosage forms for the biopharmaceutical and consumer health and nutrition industries. The company's unique combination of science, engineering, formulation and capsule expertise enables its customers to optimize the bioavailability, targeted delivery and overall performance of their products. Capsugel partners with more than 4,000 customers in over 100 countries to create novel, high-quality and customized solutions that align with our customers' evolving needs and benefit patients and consumers.

Capsugel continues to build on our decades-long track record of ingenuity, credibility and flexibility to deliver an exemplary experience and drive added value creation for our customers. Its proprietary and patent-protected technologies, extensive formulation know-how, unrivaled expertise in capsule polymer science, and product and process design capabilities help customers meet their target product profiles and commercial objectives, while allowing rapid design and development across a wide range of dosage forms, including differentiated capsules, liquids, granules/powders, pellets and tablets targeting various delivery methods.

The company's biopharmaceutical customers are continually motivated to speed the pace of discovering and developing novel products that will help improve people's lives. Capsugel is partnering with an ever-expanding set companies – both large and small – to overcome several challenges inherent in this quest. With a fundamental understanding of APIs that comes from advancing thousands of drug compounds from early feasibility studies to clinic and commercialization, predictive models and expert systems for selecting the optimal enabling technologies, we are bringing design to the CDMO space, which is helping our customers accelerate their product development cycles.

Capsugel has 13 manufacturing sites and three research and development centers in nine countries across three continents. This vast global network – and the unmatched science and engineering behind it – enables the broadest range of capsule polymers, sizes and designs in the industry, as well as the ability to offer integrated product design, development, clinical supply and commercial manufacturing services to our customers around the world. The company's diversified customer base includes companies that make branded, generic and specialty pharmaceuticals; biotech products; over-the-counter medicines; vitamins and dietary supplements.

For more information, visit www.capsugel.com and follow us on Twitter and LinkedIn.

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WWW.CAPSUGEL.COM

ENGINEERING MEDICINES TO LIFE

Capsugel®

RISING TO THE CHALLENGE

Tomorrow's complex medicines face challenges to overcome low bioavailability and optimize drug delivery. This calls for a partner with the credibility, ingenuity and flexibility to deliver both the product and process design required to make your compound a commercial reality. With a unique range of technology and integrated product development from design to commercial manufacturing, Capsugel is that partner.

CAPTISOL®
A Ligand TECHNOLOGY

Ligand-owned, Captisol® was invented in 1990 by scientists at the University of Kansas Higuchi Biosciences Center for use in drug development and formulation.

The Captisol® technology is used to address the limitations of currently marketed drugs. Eight FDA-approved, Captisol-enabled® medications are marketed by: Pfizer, Bristol-Myers Squibb, and Baxter International. Captisol® also has License and Supply Agreements (LSAs) in place with a number of pharmaceutical companies worldwide with Captisol-enabled® product candidates. Routes of administration investigated include parenteral, oral, ophthalmic, nasal, topical, oral, and inhalation.

The regulatory acceptance of Captisol® is supported by extensive safety studies demonstrating its excellent systemic safety profile. In 1999, a Type V Drug Master File (DMF) was filed with the FDA. This regulatory safety data package, which includes greater than 70 volumes, supports the use of Captisol® in parenteral formulations as well as support for other routes of delivery. Multiple FDA divisions and ex-US regulatory agencies have evaluated the data package and permitted the use of Captisol® in clinical trials.

Captisol® is an established enabling technology with substantial characterization, safety documentation and regulatory review. In 1999, a Drug Master File Type V, containing preclinical and clinical safety data for Captisol® was filed with the US Food and Drug Administration. Published in scientific articles and utilized in a number of ongoing clinical trials by leading pharmaceutical and biotech companies, Captisol® is recognized as a valuable and vital delivery technology whose use could mean the success or failure of a development program.

For a complimentary 20 g sample, please visit www.captisol.com.

Meeting the Rising Need in Delivering Biological Treatments

Enable Injections' technology is designed to meet the delivery needs of biologics treatments which comprise an increasing focus in product development. The Enable Injections on-body delivery system can address the new set of challenges and deliver these high volume, often highly viscous therapeutics to the patient in an effective, safe, and affordable means that cannot be addressed by legacy injection systems. Enable Injections is introducing their line of a new class of devices to deliver these drugs subcutaneously, by patients at home, with the potential to help revolutionize treatment of cancer, autoimmune deficiencies, blood disorders and a range of other conditions. Enable Injections intends to create market leading biologics delivery devices that meet the most pressing needs of pharmaceutical companies while enabling easy patient self-administration.

The Enable On-Body Delivery System

Founded by medical device veterans, Enable Injections develops and manufactures medical devices for convenient self-administration of high volume subcutaneous injectable drugs. The Enable on-body delivery system (OBDS) consists of a single injector up to 5 ml, 10 ml, 20 /30 ml, 40 ml, and 50 ml capacity - and associated transfer system (Syringe, Vial, or Fully-Automated Reconstitution) that intuitively transfers drug from the original primary container closure to the injector. Therefore, the system does not require any change to the primary container, ensuring further drug stability studies and new product or assembly lines are not required.

Enable's Solution for Pharma

The Enable OBDS provides the potential solution for delivery of high volume subcutaneous products to enable, enhance, and differentiate the biopharmaceutical portfolio. This can be achieved through differentiating the new innovative pipeline of pharma - such as with products of similar mechanisms of action – by improving patient compliance/persistence to therapy, or through life cycle management of current biological drug products. For relevant products life cycle management opportunities supported by use of the Enable system include facilitating the delivery of intravenous formulations to subcutaneous delivery or by reducing the dose frequency of current subcutaneous formulations through increasing the dose volume.

Enable's Solution for Patients and Healthcare

The Enable OBDS is designed for the patient to self-administer at home, potentially replacing infusions at a health facility and improving cost effectiveness of biological therapies. Additionally, the injector is designed to have a friendly looking appeal to reduce anxiety; provide the smallest profile and size for highest delivery volume; promote user mobility and be simple/intuitive to use.

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Catalent®

Catalent is the leading global provider of advanced delivery technologies and development solutions for drugs, biologics and consumer health products. With over 80 years serving the industry, Catalent employs approximately 9,500 people, including over 1,400 scientists, at more than 30 facilities across five continents. Catalent has proven expertise in bringing more products to market faster, enhancing product performance and ensuring reliable clinical and commercial product supply.

As a leader in early phase development of prescription medicines, Catalent has been involved in nearly 50% of all the new molecular entities to have received FDA-approval in the past 10 years. It has recently bolstered its capabilities and capacity with the acquisition of spray dry dispersion specialist Pharmatek, and now offers the broadest toolkit of development and bioavailability enhancing technologies available. These include OptiForm® API technology for optimizing stability and processing characteristics, OptiMelt™ hot-melt extrusion, Pharmatek™ SD spray drying, and extensive expertise in lipid-based drug delivery systems with the legendary RP Scherer Softgel technology. OptiForm® Solution Suite combines these technologies into a robust, data driven, parallel screening platform which quickly and efficiently assesses the optimal formulation pathway for small molecules with bioavailability challenges in just 12 weeks. Catalent recently expanded this offering to include OptiForm® Solution Suite Bio, which quickly screens small proteins and peptides for oral delivery potential; improving patients' experiences. Since its 2015 launch, the OptiForm Solution Suite technology has been recognized with awards a number of times, including the "Editor's Choice" award at INTERPHEX 2016 and the "Excellence in Pharma: Contract Services and Outsourcing" award at CPhI Worldwide 2016.

Catalent offers an extensive range of innovative drug delivery technologies to help improve clinical and therapeutic outcomes and product value, including Zydis® fast dissolve orodispersable tablets, OptiShell™ gelatin-free softgels, OptiGel™ Bio for oral macromolecule delivery, FlexDose™ stick-pack solutions, and extensive controlled and targeted release dose forms. Sterile technologies include ADVASEPT® glass-free injectables technology; as well as auto-injectors and pre-filled syringe solutions. Catalent has also produced OTC, nutritional supplement and beauty care products since 1933, and today partners with 20 of the leading global consumer healthcare companies to leverage these other technologies to bring innovation to consumers globally.

Catalent Biologics offers one of the broadest ranges of cell line development and large molecule analytical services in the industry, all under full cGMP conditions for new biologic entities and biosimilars/biobetters, and provides support from pre-clinical testing through to post-approval release and stability. A recently announced expansion will provide capabilities for late-stage clinical and commercial manufacturing.

Catalent's network of FDA, EMA and other locally approved facilities provides flexible manufacturing solutions with global, scalable cGMP capacity. It has proven expertise in technology transfers and product launches, custom suite models, special handling, and manufacturing technologies, with the capacity to support a wide range of small and large scale manufacturing requirements. Catalent is headquartered in Somerset, New Jersey.

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SCREEN FORMULATE DESIGN

Catalent®
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NEW
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your molecule has so much potential. we share your passion to unlock it.

As the #1 global leader in drug development and delivery, we have a passion to help you bring better treatments to your patients, faster.

Our broadest expertise and superior technologies helped optimize thousands of molecules from pre-formulation through all development stages. Our integrated analytical, clinical, and manufacturing services along with patient-centric dose design streamlines and accelerates your path to patients.

- PRE-FORMULATION / FORMULATION
- OPTIFORM® SOLUTION SUITE
- BIOAVAILABILITY ENHANCEMENT
- STABILITY & SCALABILITY
- DOSE FORM DESIGN
- MODIFIED RELEASE
- COMPLETE ANALYTICAL SUPPORT
- SEAMLESS SCALE-UP

DEVELOPMENT DELIVERY SUPPLY

Catalent. More products. Better treatments. Reliably supplied.™

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CordenPharma is your full-service partner in the Contract Development & Manufacturing (CDMO) of **APIs, Drug Products,** and associated **Packaging Services**. Through a network of fully-inspected cGMP facilities across Europe and the US organized under five technology platforms – **Peptides, Lipids, Carbohydrates & Oligonucleotides, Injectables, Highly Potent & Oncology, Small Molecules, Antibiotics** - CordenPharma experts translate complex ideas at any stage of development into high-value products.

Peptides, Lipids, Carbohydrates & Oligonucleotides

- Peptide API Production
  - Solid-phase, Liquid-phase, Hybrid Synthesis
  - cGMP & non-cGMP: Process & Analytical Development, Scale-up, Clinical & Commercial Supply
- Oligonucleotides
  - Process & Analytical Development, Clinical & Commercial Supply
  - Quality & Regulatory Support
- Lipids
- Carbohydrates

Sterile Injectables

- Aseptic Filling & Terminal Sterilization Capabilities (Sterile Solutions, Lyophilization, Pre-filled Syringes, Ampoules)
- Sterile Drug Product Formulation & Analytical Development, Clinical & Commercial Manufacturing
- Packaging & Labeling Services
- Sterile Emulsion Technology
- Large Pre-Filled Syringes
- Clinical Trial Services

Highly Potent & Oncology

- API Development & Commercial Manufacturing (SafeBridge Category 4, OEL ≤1 ng/m^3)
  - Development & Scale-up Capacity for Phase I/II Supply
- Drug Product Development & Manufacturing
  - New Development Suite (CTD2) for Mid-scale (up to 20 kg) Oral Dosage Forms
  - Sterile Liquid & Lyophilization
  - Primary & Secondary Packaging

Small Molecules

- Development & Commercial Manufacturing
  - Intermediates
  - APIs & Excipients
  - Clinical Supply from Phase I – III
- Proprietary & Generic Advanced Intermediates & APIs

Antibiotics

- Non-segregated
  - Oral APIs
  - Oral & Sterile Drug Products
  - Primary & Secondary Packaging
- Segregated
  - Cephalosporins & Penicillins
  - Monobactams
  - Primary & Secondary Packaging

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CORDENPHARMA

EXPERTS TAKING CARE

FULL-SERVICE, FULLY COMMITTED

CordenPharma is your full-service CDMO for a global market. Through our network of technology platforms and cGMP facilities for the manufacture of APIs, Drug Products and pharmaceutical Packaging, CordenPharma experts translate your complex ideas at any stage of development into high-value products.

www.cordenpharma.com

TECHNOLOGY PLATFORMS

- **PEPTIDES, LIPIDS & CARBOHYDRATES**
- **HIGHLY POTENT & ONCOLOGY**
- **INJECTABLES**
- **SMALL MOLECULES**
- **ANTIBIOTICS**

VISIT US AT

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Drug Delivery Partnerships

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THE BUSINESS DEVELOPMENT EVENT BRINGING YOU VISIONARY IDEAS, DISRUPTIVE TECHNOLOGY, AND PARTNERINGONE® TO MAXIMIZE YOUR PRODUCT LIFECYCLE AND GENERATE NEW REVENUE STREAMS

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Disruptive Innovation

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Author, The $1,000 Genome

Healthcare & Policy

Erik Paulsen
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The Future of Drug Delivery

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CRODA

Pharmaceutical formulators continue to strive to create market leading products with maximum efficacy, quality, and performance. However, the inability to achieve API solubility and stability are common day-to-day challenges for formulators. With the help from Croda's superior quality and ultrahigh purity specialty line of excipients, formulators are able to surpass these barriers, making Croda the supplier of choice in the global pharmaceutical market. With products being manufactured at multiple sites throughout the world, we are able to provide local and consistent supply of one of the widest ranges of chemical specialties, surfactants, and high-purity lipids available to the pharmaceutical industry.

Croda also provides a large span of products for topical dosage forms, as well as multi-compendial solvents, and surfactants suitable for parenteral, oral, ophthalmic, nasal, vaginal, and suppository formulations to help formulators maximize the value of their final drug product.

Croda has been actively investing in GMP API technologies and R&D to ensure the continual delivery of exceptional ingredients. We consider future health and wellness needs when creating new specialty products. Croda has developed a proprietary process called Super Refining™ to help create products of superior quality and purity. The process helps to physically remove impurities from pharmaceutical excipients and nutritional oils without altering their fundamental structure.

HIGH-PERFORMANCE PRODUCTS

Croda offers a complete range of excipients for topical dosage forms as well as high-purity solvents, vehicles, and surfactants suitable for parenteral, oral, suppository, and ophthalmic formulations. The company's products include:

- Super Refined™ Range of Excipients
  - Oils: including sesame, soybean, peanut, corn, olive, and cottonseed
  - Oleic acid: high-purity multi-compendial excipient
  - PEGs: high-purity, multi-compendial polyethylene glycols
  - Dimethyl isosorbide: high purity solvent for hydrophilic and lipophilic APIs, enhancing skin penetration
  - Polysorbates
  - Castor oil
  - Propylene glycol
  - Etocas™ 35: high-purity polyoxyl 35 castor oil
- Crodamol™ Range: a range of ester solvents and vehicles
- Polawax™: a complete compendial and self-emulsifying wax
- Synperonic™ Range: a range of monograph compliant poloxamers
- Crodacol™ Range: fatty alcohols
- Crodesta™ Range: sucrose esters for mild emulsification and sustainable release in tablet applications
- Medilan™: medicalgrade lanolin designed to surpass USP requirements for lanolin, modified

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EG-GILERO is your single-source, trusted partner for design, development and contract manufacturing within the medical device, drug delivery, and primary pharmaceutical packaging markets. Acting as a seamless extension of your own internal resources, we accelerate speed to market of innovative devices from concept straight through commercialization.

EG-GILERO is truly different from other outsource partners. Design & Development is in our DNA. Our experienced engineering team provides a full suite of design and development services for your medical device and drug delivery device product development projects. Beginning with the end user in mind, EG-GILERO conducts clinical site user research, novel concept development, smart rapid prototyping, detailed engineering, and intellectual property (IP) management. By adhering to strict design controls and our ISO 13485 certified quality management system (QMS), EG-GILERO integrates human factors engineering (HE75) and design for manufacturability (DFM) throughout the entire development process.

EG-GILERO offers a complete range of analysis and Testing services performed by our own skilled engineers and technicians in our on-site mechanical and microbiological test labs. Utilizing established testing standards, or creation of custom test methods, EG-GILERO provides testing services ranging from engineering evaluations and formative studies to complete design verification and summative user validation testing.

EG-GILERO can develop the Regulatory strategy for your product and execute on all of the required elements, providing you a path to regulatory approval. We prepare and maintain regulatory design history files, conduct risk analyses including design and process FMEA's, and develop packaging and labeling layouts for regulatory related needs. EG-GILERO routinely prepares and submits 510(k) applications to the FDA, as well as technical files for CE Marking and documentation to support new drug applications.

EG-GILERO's in-house Tooling capabilities are unique and unparalleled in the industry. Our tooling capabilities range from single cavity, pre-production, fast development molds to high cavitation, valve-gated hot runner and two-shot systems.

EG-GILERO is your trusted Contract Manufacturing partner with a breadth of capabilities and a global reach. With multiple contract manufacturing sites in North America, Dominican Republic, and Asia, EG-GILERO has established expertise in cleanroom injection molding, cleanroom assembly, and sterile barrier packaging. From manual assembly with low cost labor, to high-volume, lights out contract manufacturing, we have a solution for all of your contract manufacturing needs.

EG-GILERO's sole focus in medical devices and drug delivery devices throughout a product's entire development and commercial lifecycle, positions EG-GILERO to uniquely provide the clinical and technical expertise you have been seeking in a true partner.

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EG GILERO

We are passionate about medical innovation. Together, our highly skilled, agile team will accelerate your device timelines from concept to commercialization. As your trusted design and manufacturing partner, we are dedicated to your success.

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www.eg-gilero.com

FRONTAGE
YOUR DRUG DEVELOPMENT PARTNER

AT FRONTAGE, WHAT SETS US APART, GETS OUR CLIENTS AHEAD

Frontage is a full service CRO that closely collaborates with pharmaceutical and biotech companies to help them bring promising drug candidates to market. With 14 locations in the US and China, Frontage has been assisting clients in their drug development efforts since 2001. Spanning from preclinical through late-stage development, it's full-service offerings include DMPK, bioanalysis using 60+ LC-MS/MS instruments, analytical testing, product development, and full biometrics support.

Frontage also provides turnkey product development services to generic, innovator and consumer health companies to support IND, NDA, ANDA, and 505(b)(2) submissions. What sets us apart is our ability to collaborate closely with our clients to ensure a deep understanding of their drug development goals and our ability provide flexible solutions that are customized to each client's needs. At Frontage, we are committed to providing rigorous scientific expertise to ensure the highest quality and compliance on each project.

Frontage proudly serves innovator, generic, and consumer health companies from IND enabling through late-stage clinical projects. Frontage successfully assists clients to advance hundreds of molecules through development to commercial launch in global markets. This partnership with our clients is how we turn services into real solutions that get our clients ahead.

About our CMC (Chemistry, Manufacturing & Control) Services

With an outstanding compliance history, the CMC team at Frontage operates under strict adherence to ICH and US FDA GMP guidelines. Our facilities and processes undergo routine audits and inspections from sponsors and regulatory authorities.

Frontage's CMC portfolio of services spans the entire drug product development of oral solids, topical, and sterile, from proof-of-concept, preclinical through clinical trials and commercialization support. We have extensive experiences in formulation development, analytical method development and validation, technical transfer, and clinical trial materials (CTM) manufacturing, as well as commercial product release and stability testing for US, EU, and Asian markets.

- Analytical Method Development/Validation & Sample Testing
- Formulation Development for IND, NDA & ANDA
- GMP Manufacturing of CTM (Oral Solids, Topical, Sterile)
- Commercial Product Release & Stability Testing

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Gattefossé

We provide specialty excipients and drug delivery solutions to the health industries worldwide. With a service and distribution network that spans more than 60 countries, we ensure responsiveness to the pharmaceutical industry's needs from both regional and global perspectives.

Gattefossé Corporation serves customers in USA, Canada, and Mexico.

Products

Creating sophisticated and innovative lipid excipients is a core specialty of the Gattefossé Group. Each excipient is designed to meet a unique set of formulation and functionality objectives while conforming to the highest safety, quality, and regulatory standards. The product offer includes solubilizers, emulsifiers, bioavailability enhancers, sustained release matrix formers, and skin penetration enhancers for all routes of administration.

Formulation Development Insight

With the inauguration of the Application Laboratories in USA, we will support customers with formulation choices that stand to shorten the development path and improve the solubility, dissolution, and delivery of molecules. This is over and above our ongoing efforts that support application of lipids in formulation technologies notably SMEDDS, Sustained Release, Coatings, Granulation by extrusion or other melt techniques.

Guidance documents for excipient selection and formulation design for preclinical as well as late development stages are available upon request.

Investing in the USA

This year marks a significant surge in the Group's continued investment in the USA that accounts for a 25% increase in the number of technical and support staff, the construction of a new, state of the art application laboratory, and expansion of office space at the current location in Paramus NJ.

Core Values

The conviction that achieving an innovative edge benefits all concerned is rooted in the 135 year history of the Gattefossé enterprise. This vision is supported by continued investments in research and development and initiatives that foster knowledge sharing. Sponsoring St-Remy conferences for 50 years and AAPS scientific awards since 1990's are examples of such initiatives.

Safety, Regulatory & Quality Support

Gattefossé characterizes each excipient for physico-chemical properties and safety profiles and ensures each product has global regulatory acceptance. Every product is supported with full dossiers including safety data, regulatory standing, and updated Drug Master Files with the FDA.

Our Goal

We aim to simplify formulation decisions that minimize attrition rates and shorten the drug development path. For existing drugs that could benefit from improved dosing, better patient compliance, or extension of product life cycle, we emphasize innovative formulation technologies. For new drug entities that suffer from solubility and bioavailability issues we focus on guidance for pre-formulation decisions that may be combined with innovative drug delivery approaches.

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IMPACT ANALYTICAL
Comprehensive **Testing**. Unparalled **Service**.

Impact Analytical is a contract testing laboratory supporting all phases of medical device and drug product development and manufacturing. We offer method development, validation, stability, extractables/leachables, material characterization (physical and chemical), problem-solving, unknown identification, compendial (USP, EU, JP), and release testing services. We specialize in small molecule and polymer characterization, and have over 50 years of experience providing research and development support.

Our 17,000-sq-ft facility test laboratory was designed to match our work process, which reduces risk of sample contamination and maximizes project throughput. We utilize state-of-the-art equipment, including UPLC, exact mass Q-TOF LC-MS, and ICP-MS to deliver accurate and precise data. We offer testing in the following areas:

Molecular Characterization
Mass Spec, NMR, FT-IR, UV

Liquid Chromatography
HPLC, UPLC with UV, CAD, MS Detection; Ion Chromatography

Gas Chromatography
GC with MS, FID, TCD, and ECD Detection

Wet Chemistry
KF, Chloride, and Potentiometric Titration, pH

ICP
ICP-MS, ICP-OES

Microscopy
Optical

Thermal/Mechanical
TGA, DSC, Viscosity

Sample Storage
ICH conditions 25oC/60%RH, 30oC/65%RH, 40oC/75% RH

We provide testing support services to all sizes of medical device and pharmaceutical companies – from virtual to large, global providers. Our moderate size allows us to be flexible to meet the needs of small and mid-size companies, and our full breadth of offerings gives us the tools to meet the diverse needs of large companies.

Impact Analytical has a mature quality program. We are cGMP registered, GLP compliant (FDA, EPA), ISO 9001 certified, and DEA licensed. We are regularly audited by the FDA and EPA with no findings (483s), and routinely host prospective and current clients for successful facility audits.

Our customer-focused approach differentiates us in the industry and ensures you receive high-quality results that are on-time and on-budget. Our mission is to meet the needs of the customer in every way. Please contact us to schedule a facility audit and/or to discuss your next project.

IMPACT ANALYTICAL
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Insulet Corporation

Insulet Corporation is an innovative medical device company based in Billerica, MA. Insulet designs and manufactures the Omnipod® Delivery System, an intelligent wearable subcutaneous pod used in a variety of therapeutic areas. A proven technology with insulin delivery for over 10 years, today Omnipod offers a versatile alternative for delivery of early phase and commercially marketed drugs and biologics. This automated drug delivery system could help offer improved adherence, outcomes, and differentiation throughout a product's lifecycle.

With its ability to automatically administer the precise dose of medication, at the exact time without manual input, Omnipod helps ensure optimal delivery and adherence with minimal interruption to a patient's lifestyle.

Insulet Corporation has combined the efficacy of pump delivery with smart technology in its Omnipod Delivery System. Contrary to traditional technologies, Omnipod is a wireless and tubeless drug delivery system that provides pharmaceutical and biotechnology companies with a convenient and innovative way to administer drugs outside the healthcare setting. It can help these companies bring to market more personalized delivery methods, increasing options available for harder-to-manage diseases and patient satisfaction.

The Omnipod works by simply placing the device anywhere on the body that is considered an injection site. Using either a handheld remote or via automatic internal activation, the device deploys a cannula into the skin and begins administering medicine at the specified dose, rate, and time.

Offering a fully customizable dosing profile, the Omnipod Delivery System can be tailored to the ideal solution for the drug delivery. The intelligent dose management system can allow the drug to be delivered at specific intervals as defined by the drug manufacturer, clinician, or patient.

Insulet Corporation works in partnership with drug companies to ensure successful adoption of the Omnipod Delivery System and its smart technology. Equipped with a soft delivery cannula for a virtually painless experience and adhesive backing for extended wear, Omnipod is the on-body device that allows patients to live life uninterrupted.

INSULET CORPORATION
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LATITUDE Pharmaceuticals Inc. is a leading-edge research boutique that provides innovative drug formulation development services to the human and animal health biotech/pharmaceutical industries. Since our founding in 2003, we have completed more than 700 client projects and established a reputation for successfully formulating highly insoluble compounds – a problem attributable to 40% of new drug development failures.

Expertise

We are formulation specialists who overcome the tough formulation challenges of problematic compounds, and we have built our reputation on a track record of creative approaches, reliability, rapid turnaround, and client satisfaction. LATITUDE's extensive experience and technical strengths in a wide range of dosage forms are applied to help our clients successfully address even the most difficult formulation challenges.

LATITUDE's background, experience, and unique internally developed technologies are applied to solve problematic formulation issues, such as insolubility, poor absorption, poor taste, and/or vein irritation that are often encountered.

In addition, LATITUDE develops its own proprietary drug products by re-formulating existing drugs, thereby improving efficacy, safety, and overall therapeutic value. We are proactive in forming strategic alliances and out-licensing new reformulated drug products.

Drug Delivery Platforms

Nano-E (Nanoemulsion)
- A versatile solubility-enhancing platform for oral/injectable liquid formulations, ideal for highly insoluble APIs or "brickdusts"

PG Depot (Phospholipid Gel Depot)
- Allows a customizable release profile of a subcutaneously-administered drug over 1-7 days
- Injectable through fine (up to 28 G) needles for easy subQ administration

ARTSS (Aqueous Room Temperature-Stable Solutions)
- A platform for the transformation of lyophilized powders or 2-8°C solutions into RT-stable aqueous solutions

RFAP (Rapidly-Dissolving Amorphous Powders)
- Creates a stable, amorphous, water-soluble powder that keeps the API from reverting to the crystalline state

24H (All-Day 24-hr ER Tablets)
- An oral tablet platform for increased dosage and linear, sustained release of drugs for up to 24 hours

MiniSpheres
- Novel delivery format for high/bulky dose oral drugs and/or sustained release

GelPatch
- Novel transdermal spray/rub-on gel that dries as durable patch to provide multiday drug delivery

Feedlets (Animal Health)
- Controlled-release, taste-masked pellets or chewables that can be easily administered in animal feed

Contact us for more information and to discuss how LATITUDE can address your formulation needs.

LATITUDE PHARMACEUTICALS INC.
9675 Businesspark Avenue - San Diego, CA 92131
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NEMERA
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E : information@nemera.net W: www.nemera.net

With over 1,500 people and 4 plants across two continents, **NEMERA** is a world leader in the design, development, and manufacturing of drug delivery devices. Nemera provides solutions for the pharmaceutical, biotechnology & generics industries, from full solution development to pure contract manufacturing, through customized solutions.

Nemera's expertise covers multiple modes of delivery:

- OPHTHALMIC: Nemera offers a multi-dose closing tip system, Novelia®, which avoids the need for preservatives in the drug and prevents bacterial contamination over the duration of treatment. Novelia® represents a major innovation in ophthalmic drug delivery by providing a preservative-free alternative for chronic treatments in a patient-friendly package. It is commercialized for both Medical Devices and Prescription drugs across 4 continents. The Novelia® system is the first and only preservative-free multidose eyedropper UK-approved for a glaucoma drug.

- NASAL, BUCCAL, AURICULAR: Nemera offers an extensive range of metered pumps and valves, compatible with a wide choice of actuators in different shapes and fitments for nasal, buccal and auricular delivery. SP270+ is the new optimized spray pump engine for ear, nose, and throat in terms of performance and raw materials. Advancia® embodies a major breakthrough in nasal drug delivery by providing patients with a user-independent device in a user-friendly package and exceeds regulatory requirements. The Advancia® innovative project is co-financed by the European Union. Europe is committed in Normandy with the European Regional Development Fund (FEDER).

- PARENTERAL: Nemera leverages decades of manufacturing and development experience in the parenteral device segment (auto-injectors, pens, safety devices, and implanters). Nemera has developed Safe'n'Sound®, a fully passive safety device for prefilled syringes to aid in the protection of healthcare professionals, patients who self-inject doctor- prescribed medications, and individuals that assist self-injecting patients, from accidental needlesticks. Nemera developed also Safelia®, an innovative autoinjector, declined in 1-ml and 2.25-ml platforms for prefilled syringes. Safelia® is able to administer high volumes, high viscosities, and through thinner needles.

- DERMAL & TRANSDERMAL: Nemera's dermal delivery devices have been designed to ensure patient compliance thanks to precise and consistent dosing, which is critical especially when applying formulations for systemic treatments. Sof'Bag® is a high-performing airless pouch system for dermal and transdermal applications. Sof'Airless XS is a protective mini-airless system for small dose applications and sampling. Sof'Airless XL is a customized dispenser for higher dose applications.

- PULMONARY: Nemera has a long-standing expertise in designing, developing and industrializing pulmonary devices (pMDIs, DPIs).

LifeSciencePR, a spin-out of well-established SGW Integrated Marketing & Communications, is a full-service lifescience marketing and communications agency specifically assembled to address the unique challenges, issues, and opportunities of emerging and innovative life science companies. Our experienced staff knows what it takes to break through with your breakthroughs! Whether it's capital, co-development partners, a step up in valuation, etc., we can power your engine in your continued drive toward your financial and corporate objectives.

Public Relations/Media Relations - Working as your sole strategic partner or as an extension of your communications staff, our dedicated team has the direct industry experience and knowledge necessary to develop your unique message and target only the most appropriate B2B vehicles that will result in the most valuable editorial coverage.

Investor Relations - IR is a strategic management responsibility that integrates finance, communication, marketing, and securities law compliance to enable the most effective two-way communication between a company, the financial community, and other constituencies, which ultimately contributes to a company's securities achieving fair valuation. We can help, whether it's capital raising, financial community meetings and contacts, and traditional or internet corporate communications.

Social Media Development/Management - Promote your business through the major social media channels via all leading social media platforms, blogs/RSS, viral content, online communities, news aggregators, and social influencers the smart way! We can help effectively engage with your online audience, both present and potential, by developing and executing a comprehensive Social Media Plan based on your specific requirements.

Multimedia/Interactive/Web Design - Building web applications that help your business run and grow takes a set of unique skills and talent. We can be your architect, project manager, analyst, designer, developer, internet marketing specialist, social media strategist, quality assurance tester, and hosting support staff.

SEO/SEM - Today, more marketers are realizing SEM and SEO are not separate disciplines. Instead, they are complementary programs that can benefit each other to increase conversion rates and share of voice. SEM and SEO teams should work together to improve results on their respective programs, increase return on search marketing investment, and drive a lasting lift in conversion across the board. Let us show you how.

Advertising Design - We employ unique, big picture solutions that get to the heart of the real advertising issues, challenges, and opportunities facing the ever-evolving B2B life science industry. Our specialized active and passive campaigns (online or print) and collateral design/corporate ID positioning, including logo development and branding, accommodate any size budget and are geared directly toward complementing and supporting your life science business development initiatives.

Traditional/Online Media Planning & Placement - Analyzing, planning, and buying media is a time-intensive, multi-pronged approach that requires dialogue with the client, defining the target audiences, focused research, a media strategy that maximizes efficiency of the available budget, and strategic placement capabilities.

Tradeshow/Event Planning - Access to potential clients is at an all-time high, so let us help you ensure your competitive advantage through our tradeshow & event logistics management, booth design capabilities, high-tech lead generation, and promotional materials.

Research & Focus Group Services for:
- Brand Development
- Client Perception

Building a world-class brand and a positive effective perception doesn't happen by chance. It's a purposeful endeavor that is rooted in the fusion of disciplined, strategic thinking and execution. The result is an asset that drives your business ahead. Our strategic platform and architecture will get you there!

Full Service Video Production - Through the years, we've created the commercials, videos, social media content, multi-media presentations and animation used in all of SGW Integrated Marketing Communications / LifeScience PR integrated strategies and distribution touch points. In 2016 we re-organized the division, made significant investments in equipment, our facilities and people. Our working philosophy is simply to operate smarter, faster and more efficiently for our clients. And while we're very proud of the hundreds of creative awards we've won over the years, we're much prouder for the successful results we deliver for our clients.

LIFESCIENCEPR
219 Changebridge Road
Montville, NJ 07045
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Smarter. Faster. Easier.

- Public Relations
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- Investor Relations
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- Media Planning and Placement
- Multimedia/Web Development
- Social Media Development/Management
- Search Engine Optimization/Marketing

Get Noticed. Get Funded. Grow Faster.

When you need to connect with investors, business partners and regulatory agencies, LifeSciencePR can make that happen. Our integrated communication strategies and well-established industry contacts will help your emerging life science company achieve its short and long-term corporate objectives.

We work seamlessly with your senior management team to develop the most effective communication initiatives to reach your prospective investors and partners.

LifeSciencePR will get you there smarter, faster and easier than any other marketing and communications firm in the industry.

Call us at 800.724.2372 or visit lifesciencepr.net.

LifeSciencePR

we'll get you there.

CORPORATE DESCRIPTION

A dedicated staff supports clients bringing new products to patients and improving existing products and operations. Clients gain with successful development and clinical manufacturing, bridging discovery through product approval and commercial manufacturing. A talented, dedicated staff skilled with experience is coupled with well-equipped laboratories and flexible manufacturing capabilities. Support services span product development, process engineering, clinical manufacturing and technical service. Internationally recognized as an industry leader, clients have fostered our reputation for providing innovative solutions, achieving desired results, and exceeding expectations. This reputation is demonstrated by collaborative relationships with clients for over 24 years.

MAJOR PRODUCTS/SERVICES

Capabilities

- Pre-clinical through Phase III Clinical Materials, lyophilized/liquid products
- Containment for cytotoxic/high potent products
- Dedicated/disposable equipment
- Vials: 2 to 160 mL: novel delivery systems
- Cartridges/syringes: 1 to 50 mL
- Lyophilizers: 0.2 m2 to 4.5 m^2
- Nucleation On-Demand Technology
- Bulk Lyophilization
- Batch sizes: up to 75L
- Drug and Device Registration/DEA license
- US/EU compliant

Services

LTI successfully developed formulations, processes or prepared clinical material for over 873 diverse products:

- Anti-infectives
- Human/Recombinant Biologics
- Vaccines
- Nanoparticles/emulsions
- Oncolytics/HPCs
- Small Molecules/Therapeutics
- Diagnostics
- Bioengineered materials

Development Sciences

Development Sciences focuses on formulation through product characterization. The Process Lab provides capacity for small to medium scale lyophilization. Filtration, filling, stoppering, and loading the qualified pilot-scale lyophilizers are in certified Class A/100 environments, emulating aseptic manufacturing conditions.

- Thermal Analysis
- Product Design
- Formulation Development
- Product/Process Feasibility
- Cycle Design/Refinement
- Product Characterization
- Toxicology Material
- Stability Batches

Clinical Manufacturing

US/EU compliant Clinical Manufacturing Area (CMA) for preparation of clinical material is for processing a wide range of products, including those having unique requirements. The CMA includes an aseptic suite featuring advanced containment/isolation technology using unique disposable negative pressure isolators for, inspected and approved for handling BSL-2, cytotoxic and highly potent material.

- Aseptic compounding
- Pre-clinical through Phase III
- Small to medium batch sizes
- Liquid/diluents

Technical Services

Technical services are available providing support for all aspects of lyophilization.

- Customized Training
- Qualification/Validation Support
- Investigations
- Quality/Compliance

MAJOR MARKETS

Working synergistically, over 458 emerging companies and multinational corporations throughout the world have engaged our support in successful collaborations for a variety of projects. These projects span initial product and process development for new entities right out of drug discovery, preparing Phase I and II clinical material, technology transfer to commercial manufacturing and gaining regulatory approval. Gaining an international reputation, projects are with clients in US, Canada, Mexico, Puerto Rico, Eastern and Western Europe, Australia and Japan.

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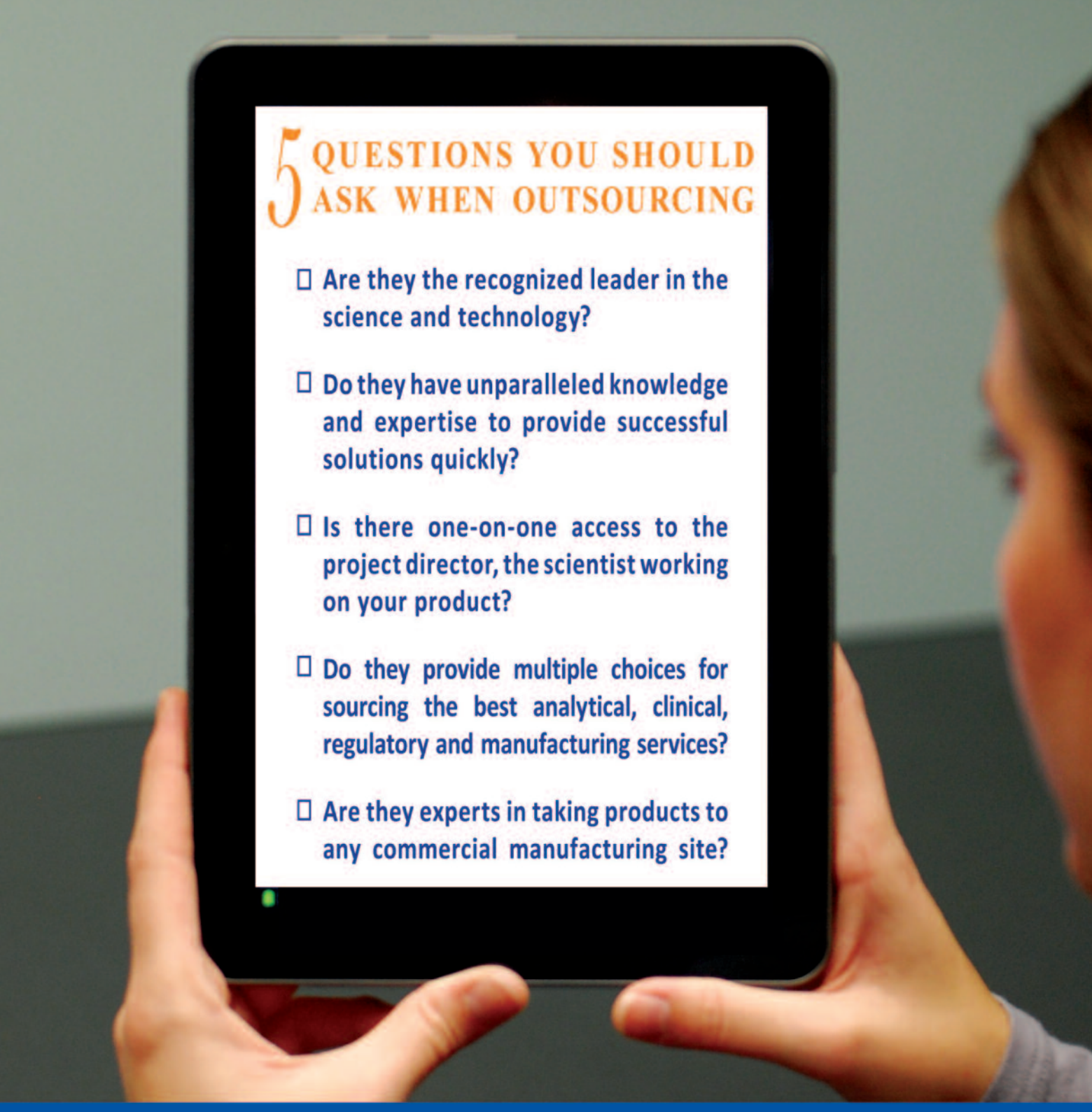
30 Indian Drive
Ivyland, PA 18974-1431
T: (215) 396-8373 F: (215) 396-8375
E: inquiry@lyo-t.com W: www.lyotechnology.com
Year Founded: 1992



Benefit from the focused expertise gained from working on 873 diverse products, collaborating with 458 companies over 24 years.

Talk with the people who can provide you the right answers

Development Sciences Clinical Manufacturing Technical Services

LYOPHILIZATION TECHNOLOGY, INC.
Integrating Science and Technology

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PHONE +1 (215) 396-8373 • Fax +1 (215) 396-8375
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metrics contract services

Company Overview

Metrics Contract Services is a full-service pharmaceutical development and manufacturing organization serving clients worldwide. We deliver proven scientific and operational excellence for oral dosage forms. Today, as a subsidiary of Mayne Pharma Group, we offer clients more resources and capabilities than ever before.

Pharmaceutical Development

We offer comprehensive formulation development services from preclinical through Phase III CTM including: tableting, immediate release, modified release (including controlled/matrix and sustained release), capsule filling, over-encapsulation, milling, micronizing, enteric coating, spray drying, extrusion, and spheronization. Our facilities and processes are designed to handle potent products, cytotoxic compounds, and controlled substances.

Analytical Services

With more than 100 chemists on staff, Metrics analyzes the physical and chemical characteristics of drug substances and drug products through development and validation of methods, release and stability testing. We perform this work in compliance with industry standards and international regulatory guidelines.

Potent Products

Our segregated potent facility provides total engineered containment through customized, hard-wall isolation technologies. Containment is achieved at 30 nanograms per cubic meter of room air; equipment and change parts are dedicated exclusively to potent use. The facility features independent entry, exit and equipment double airlocks, decontamination showers, dedicated wash-room, dedicated equipment storage and pass through for product/waste.

Fast-Track First-Time-In-Man (FTIM) Studies

Metrics Contract Services has successfully delivered materials for over 150 FTIM studies. Our process ensures speed and quality, with a 16-24 week timeline from receipt of well-characterized NCE to shipment to the clinic. Services include stability studies, analytical methods development and validation. Choose simple formulation, blended powder in capsule, or neat API in a bottle.

CTM Phase I, II, III

Our CTM capabilities offer capacity for all clinical trial phases. Our state-of-the-art, flexible manufacturing facility and equipment can handle up to 450-kilo batch sizes. We also offer expertise in over-encapsulation for comparator studies, as well as potent drug handling capabilities. CTM packaging is also available.

Stability Storage

Metrics Contract Services is investing $3.5 million in a 15,000-sq-ft stability storage expansion that will triple its current capacity. The expanded stability storage facility is being constructed with automated emergency power generation to ensure integrity of stored samples, with system redundancies maintaining environmental controls in all circumstances.

Concept to Commercialization

The parent company of Metrics Contract Services, Mayne Pharma, is investing $80 million to significantly expand facilities and equipment at its site in Greenville, NC. The strategic capital investment will fund a new 126,000-sq-ft, oral-dose commercial manufacturing facility, quadrupling the company's US manufacturing capacity, and the re-purposing of space to create 10+ new analytical laboratories and formulation development suites.

The new facility means Metrics Contract Services can offer a more complete "concept to commercialization" solution in one contiguous location for clients, providing larger scale and increased capabilities for seamless scale-up, eliminating the need for site transfers.

METRICS CONTRACT SERVICES
1240 Sugg Parkway
Greenville, NC 27834
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E: thomas.salus@maynepharma.com W: www.metricscontractservices.com

From Concept To Commercialization. Now Metrics Delivers Across The Spectrum.

With an $80 million expansion underway, Metrics Contract Services will soon be your solution for oral-dose pharmaceutical development through commercial manufacturing – all in one contiguous location. No site transfers. And the same great customer experience our clients have come to expect.

Customers will also find expanded and improved state-of-the-art potent facilities designed to meet regulatory requirements of international agencies. At Metrics, we're committed in our pursuit to be the most sought-after oral-dose CDMO.

Find out why there's never been a better time to talk to Metrics. To learn more, visit MetricsContractServices.com/expansion.

Formulation Development • Analytical Testing • Commercial Manufacturing

Greenville, NC, 252-752-3800, www.metricscontractservices.com

metrics contract services

Minnesota Rubber & Plastics
Quadion LLC

Creating Value With Innovative Solutions

Minnesota Rubber and Plastics provides over 65 years of injection molding and manufacturing experience. Because of our unique ability to offer both rubber and plastic combination components, including complete assemblies, we can offer greater engineering design and production efficiencies, thereby reducing development time, minimizing costs, and decreasing your time-to-market. Our materials are compliant with ISO 10993, USP Class VI, and FDA requirements, and we operate an ISO 13485:2003-certified quality management system.

What's more, we know how to maintain the integrity of your basic design while taking into consideration factors, such as shrink distortion and parting lines. As the relationship between materials, parts, and end-use performance need to be addressed, we also know how to solve problems arising from torque valves and sealing contacts. We then ensure that the rubber and plastic materials complement each other's tolerance capabilities. Once the design is complete, we can follow through with testing using tools, such as FEA, where benefits include increased strength, decreased material usage, and reduced costs.

Design Services

Our state-of-the-art facilities offer comprehensive design services that advance your programs:

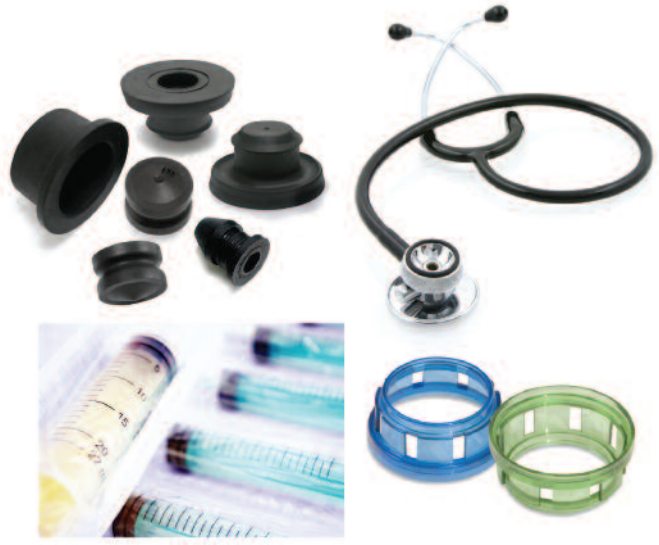
- Preliminary engineering assistance
- Mechanical design review
- Materials engineering
- Materials R&D
- Specialty compounds
- Rapid mold design and development
- Complete prototype services
- Design engineering
- Metal-to-Plastic conversions
- Rubber-to-TPE conversions
- Plastic-to-Plastic
- Process engineering
- Mold flow analysis
- Functional testing
- Leak testing
- Assemblies

LSR (Liquid Silicone Rubber) Molding

- Excellent heat resistance up to +225°C/437°F
- Good resistance to steam, ozone, UV light, radiation and weathering
- Excellent electrical resistance
- Good resistance to aging
- Physical inertness
- High mechanical strength
- Thermoset material

Quniton® Technology

Reducing Friction Quniton® serves as a highly lubricious material compound with performance capabilities uniquely designed to improve and withstand application needs. Formulated to have a low coefficient of friction, it resists bonding or sticking to a wide range of materials diversifying interface capability. Enhancing Product Lifespan Quniton® possesses non-reactive properties that ensure consistent surface to surface contact over time retaining chemical and thermal stability.



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FRICTION REDUCING. ENHANCE YOUR PRODUCT LIFESPAN WITH Quniton®

Quniton®

Quniton® – The NEW, highly lubricious material portfolio.

It has performance capabilities uniquely designed to improve and withstand Medical and Pharmaceutical application needs. Formulated to have a low coefficient of friction, it resists bonding or sticking to a wide range of materials and diversifying interface capability. Enhancing product lifespan, Quniton® possesses non-reactive properties that ensure consistent surface-to-surface contact over time, retaining chemical and thermal stability.

Industry applications:
MEDICAL & PHARMA •Plunger and Caps •Valves •Pumps •Seals •Syringe Plugs •Vial seals •Catheters •Connections •Diaphragms

Call 952.927.1400 or visit www.mnrubber.com

Minnesota Rubber & Plastics
Quadion LLC

MULTISORB Technologies

Success Through Efficiency℠

Driving your success and quality through the optimal use of sorbent technology

Selecting the optimal sorbent for your pharmaceutical, diagnostic, or dietary supplement product makes a difference. Poorly designed sorbents can result in downstream quality issues, inefficient operations and overall increased costs. At Multisorb, we offer solutions to help you quickly and efficiently select the most effective sorbent for your product, avoiding costly mistakes.

By examining the entire development process in three key areas – Identify, Select and Dispense – we optimize each stage of the process to help you better achieve desired results for healthcare product protection and shelf life while reducing your overall costs.

Identify: Optimize Product Stability

Using SimulSorb and SimulOx, our Quality by Design (QbD) based pseudo-empirical modeling, our scientists efficiently identify the optimal sorbent formulation required to meet your product's desired shelf life. Our simulations provide solutions for moisture, oxygen or volatiles management based on parameters specific to your product including degradation profile, packaging materials, sorbent type and required stability profile. By quickly identifying your sorbent formulation, you can eliminate costly sorbent ranging studies and speed time-to-market by 6-12 months.

Select: Sorbents for all Packaging Formats

Our technical team will help you select the optimal sorbent delivery format to provide the most efficient packaging presentations. With sorbent formulations available in multiple standard and customizable formats, we can meet the specific requirements of all your packaging applications and optimize your sorbent configuration.

Dispense: Systems for Turnkey Operations

With corresponding dispensers designed by our engineers for our sorbent solutions, we provide unparalleled advantages of a Systems Approach, including seamless integration of sorbent placement into your product packaging and an industry leading output efficiency of >99.997% that delivers the lowest total cost of ownership for sorbent dispensing applications.

Solutions Designed to Meet Your Needs

At Multisorb, we realize it takes more than a one-sized-fits-all approach to meet the complex needs of pharmaceutical and healthcare companies. That's why we provide our customers with end-to-end solutions to help package and protect their healthcare products through innovative and reliable solutions. With over 650 employees worldwide, we are dedicated to delivering the highest quality and most innovative sorbent products on the market, offering full R&D, engineering, quality, and manufacturing support. Contact us today to learn more.

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W: www.multisorb.com

MULTISORB Technologies

StabilOx® Oxygen Absorbing Packets and Canisters for Pre-Filled Syringes

Is Oxygen Degrading Your Parenteral Drug Product? Protect It With StabliOx Oxygen Absorbers.

Multisorb's solutions increase shelf life by absorbing oxygen:

- Permeating into the package
- Within packaging headspace
- Dissolved in solution

Available in both canister and packet formats for easy integration into high speed packaging lines.

With over 50 years of experience, we offer a full range of sorbent solutions manufactured in compliance with 21 CFR Parts 210-211 (cGMP).

www.multisorb.com

Noble®, the leader in onboarding and device training, is a full-service, patient-centered product development and manufacturing company. Noble works closely with the world's leading pharmaceutical and biotechnology companies to develop educational and training solutions designed to provide positive patient onboarding experiences, reduce errors, and improve patient outcomes. Cross-disciplinary designers and engineers provide fully customized solutions from the first concept sketch through production, in both regulated and non-regulated environments. Noble uses ISO 9001 and ISO 13485 supply chains and manufacturing facilities.

Connecting Patient Onboarding With the Patient Journey

The first 30, 60, and 90 days, commonly referred to as onboarding, are the most important regarding patient adherence. This is the time when a patient is expected to self-administer medication based upon prescribed regimen. While a patient's first exposure to a drug delivery device typically consists of training with a healthcare professional onsite at a medical facility, a patient will most often perform medication administration alone outside of a healthcare facility and without healthcare provider supervision.

There are many variables contributing to patient adherence and therapy acceptance during onboarding, including anxiety, confidence, memory, and understanding the correct administration technique. These patient factors can detrimentally influence attitudes and perception toward medications and drug delivery devices, resulting in training gaps and treatment barriers.

Injection & Respiratory Device Training

As the number of patients required to self-administer medication increases, so does the need for patient-centric training and education, including training devices such as autoinjectors, prefilled syringes, wearable injectors, and respiratory platforms.

Noble has developed a wide variety of patient-centric onboarding products to help patients administer correctly and improve adherence and patient outcomes. Noble's offerings range from mechanical training devices to smart error-correcting training platforms, assistive devices, and even patient support including travel packs and training instructions for use (IFU).

These devices have been designed to mimic actual commercial drug delivery devices while being a low-cost reusable solution to safely and effectively onboard users.

Injection Product Features – AI, PFS & Wearable Trainers:

- Off-the-shelf and customized solutions, including proprietary technologies
- Technologies range from resettable mechanical to smart features, such as sensors, audio, and error-correcting
- Trainers designed to mimic actual device characteristics
  - Shape and design
  - Needle insertion simulation
  - Forces: cap, unlock, actuation, breakout and glide
  - Sound replication
  - Plunger replication
  - Post injection safety

Respiratory Product Features – MDI & DPI Trainers:

- Off-the-shelf and customizable solutions, including proprietary technologies
- Technologies range from resettable mechanical to smart features, such as sensors, audio, and error-correcting
- Trainers designed to mimic actual device characteristics
  - Shape and design
  - Inhalation forces
  - Sequence

By providing patients a better understanding of a device, with the ability to practice administration technique as often as needed, trainers help promote positive onboarding experiences and empower patients to lead healthier lives. In the patient-centric era, companies providing reusable, device-comparable training products will be well positioned for competitive differentiation through improved patient satisfaction, adherence, and outcomes.

NOBLE
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E: info@gonoble.com W: www.Gonoble.com

Device training happens here.

There's life beyond chronic conditions. Distractions, anxiety and understanding correct administration technique can all affect compliance. Studies suggest 61% of patients don't completely read the IFU[1] and 12% of patients have proficient health literacy.[2]

Will your patients correctly administer their drug delivery device?

noble®

Onboarding and Device Training

GONOBLE.COM 888.933.5646

Reference: 1. Noble. (2015, November). The link between device training and patient compliance. Poster session presented at PDA - Universe of Prefilled Syringes 2015, Vienna, Austria. 2. Kessels, R. P. (2003, May). Patients' Memory for Medical Information. Retrieved from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC539473/

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Patheon is a leading global provider of pharmaceutical development and manufacturing services. With approximately 8,000 employees across 26 locations around the world, Patheon provides a comprehensive, integrated and highly customizable set of solutions to help customers of all sizes satisfy complex development and manufacturing needs at any stage of the pharmaceutical development cycle. A Healthier World. Delivered.

Patheon serves as a critical partner for customers who increasingly rely on customized formulation, development, and manufacturing expertise to address growing drug complexity, cost pressures, and regulatory scrutiny – partnering with many customers early in the drug development process, and extending the relationship as molecules progress through the clinical phase and into commercial manufacturing. The breadth of services, reliability, and scale address customers' increasing need to outsource and desire to reduce the number of supply chain partners while maintaining a high quality of service.

Through the company's end-to-end integrated service offering, known as "Patheon OneSource™," customers have access to comprehensive solutions for both small molecule and large molecule biological pharmaceuticals across Patheon's three main segments, including development and manufacturing services for API (Drug Substance Services, or DSS), formulation development and preclinical and clinical drug product manufacturing (Pharmaceutical Development Services, or PDS), and commercial drug product manufacturing and packaging (Drug Product Services, or DPS).

The end-to-end integrated service offering provides a comprehensive suite of capabilities across different drug formulations to address customers' needs. These specialized capabilities address 75% of all pharmaceutical dosage forms, with expertise and specialized capacity in high-potency, controlled substances, low-solubility, sterile, modified-release and softgel technologies.

Drug Substance Services (DSS): Patheon is a leading provider of complex small molecule active pharmaceutical ingredient (API) and flexible outsourced manufacturing solutions for large molecule API, from early development through commercial scale production. The company is one of the top three outsourced manufacturers of highly complex biological drug substances, with four biologics API facilities positioned to service 70 percent of the market.

Pharmaceutical Development Services (PDS): Patheon is the number one global provider of formulation services. The company's capabilities span the full breadth of advanced scientific services from discovery to regulatory approval, including formulation development across approximately 40 dosage forms, as well as analytical services and life-cycle management.

Drug Product Services (DPS): Patheon is the number one provider of contract drug manufacturing services. Over the past decade, the company has developed and manufactured 20% of the top 100 drugs and 75% of the dosage forms on the market.

The company serves a highly diverse customer base composed of more than 400 clients, including all of the top 20 largest pharmaceutical companies, 18 of the 20 largest biotechnology companies, and 15 of the 20 largest specialty pharmaceutical companies, having provided development and manufacturing services for approximately 700 products and molecules.

Brilliant discoveries. Delivered.

We are Patheon, and we bring to bear 40 years of experience and expertise, from development to manufacturing. We also bring global reach. An industry reputation for being right on time, the first time. Supply chain solutions designed to simplify complexity and speed up the process. And a passionate belief that together we can make the world a healthier place.

Patheon

A HEALTHIER WORLD. DELIVERED.

Pfanstiehl is the premier manufacturer of cGMP high purity, low endotoxin injectable- grade excipients and biopharmaceutical components for upstream bioprocessing, downstream formulation, and specialty applications. In addition, Pfanstiehl is a leading contract development and manufacturing organization (CDMO) specializing in the isolation, purification, custom synthesis, and scale-up development of small molecule Active Pharmaceutical Ingredients (APIs), in gram to multi-ton commercial quantities. While most ingredient manufacturers or resellers focus on other industries, such as food, cosmetics, agriculture, and/or nutritional supplements, offering only a subset of "pharma- grade" ingredients, Pfanstiehl is Pharma Grade through and through. It's all we do. Pfanstiehl's ICH Q7-compliant manufacturing facility is centrally located just north of Chicago, and only 35 minutes by car from O'Hare International Airport.

Pfanstiehl's tried and true, platform-enabling protein and cell membrane stabilizers include Trehalose, Sucrose, and Maltose. Parenteral-grade, multi-compendial Mannitol is also offered as a key tool for formulation optimization. We are planning to expand this portfolio to include other key excipients based on feedback from our clients who want real cGMP manufacturing from a company that understands and supports their requirements. Many clients are not simply looking for a high-quality source of consistent ingredients, but seek a partner who can adapt to the ever-evolving regulatory landscape and address emerging formulation challenges collaboratively.

For upstream applications, Pfanstiehl manufactures high purity, low endotoxin galactose for reduction of lactate and ammonia production. Overall cell culture performance improvements can be achieved with optimized titration of galactose in lieu of other carbon sources. Pfanstiehl offers multiple types of galactose, including a non-animal- derived product. Mannose was launched in 2014 as a high purity cell culture supplement to improve native glycosylation and improve consistency in product quality attributes, particularly in high titer processes. Trehalose can be utilized in upstream bioprocessing and cell therapy applications to reduce protein aggregation and improve cell robustness.

Pfanstiehl was founded in 1919, and will soon celebrate its 100-year anniversary as a leader in carbohydrate and process chemistry. Pfanstiehl's customers include most of the world's leading biopharmaceutical and pharmaceutical companies. Our products are utilized in market-leading drugs that treat life-threatening and debilitating diseases, including cancer, rheumatoid arthritis, STDs, and diabetes. Increasing regulatory and quality requirements are benefiting high integrity biopharmaceutical and pharmaceutical suppliers like Pfanstiehl with high purity, strong cGMP controls and a strong reputation with FDA and other regulatory agencies.

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Drug Development® & Delivery

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PharmaCircle is a leading provider of authoritative information, global insight, and expert analysis on the pharmaceutical, biotech, drug delivery technology and device, and animal health industries.

PharmaCircle's premier database tracks drugs, biologics and combination products in all stages of development, connecting pipeline and product information with formulation and component details. The database delivers seamless integration of scientific, clinical, safety, regulatory, manufacturing and commercial information, and detailed analyses on over 5,750 drug delivery technologies and delivery devices.

PharmaCircle provides the broad and deep global coverage, and powerful search and analysis tools needed to answer challenging questions so you can uncover new opportunities and make informed decisions.

Key content and capabilities include:

- Pipeline & Products Intelligence
- Drug Delivery Technology Analyses
- Company Capabilities Profiles
- Business Prospecting Tools
- Trial Landscape Insights
- Formulation & Excipient Details
- Strategic Deals Analyzer
- API Manufacturers Finder
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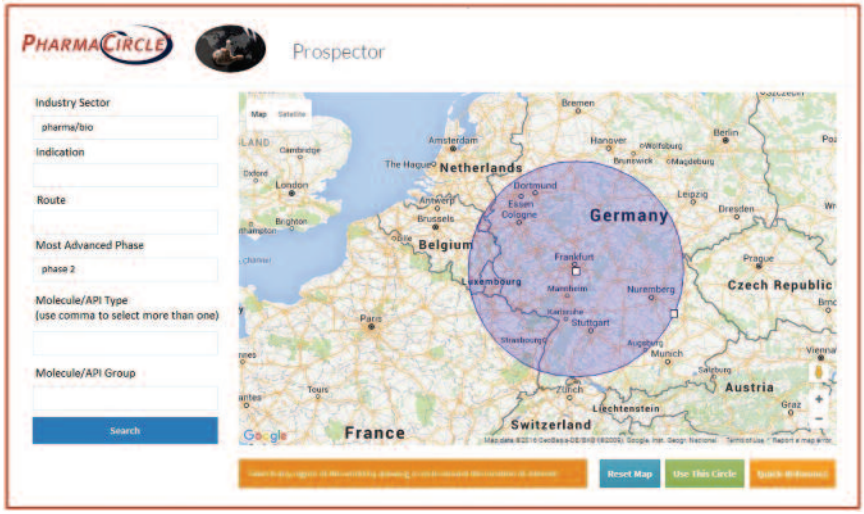
To learn more about how PharmaCircle can help your company, please visit our website: www.pharmacircle.com.



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Pharma Business Intelligence & Prospecting At Your Fingertips

PharmaCircle Business Class Solutions deliver a comprehensive view into drug, biologics and combination product development and innovation worldwide, and a combined scientific, regulatory and commercial perspective of the competitive landscape.

Business Class Professional

With an intuitive search interface and easy-to-use business prospecting and watch list apps, Professional examines more than 130,000 pipeline programs and marketed products and the business portfolios and transactions of 15,000 public and private companies.

Professional's integrated view and in depth analysis of pipelines and products includes:

- Molecule pharmacokinetic data and physical chemical structures
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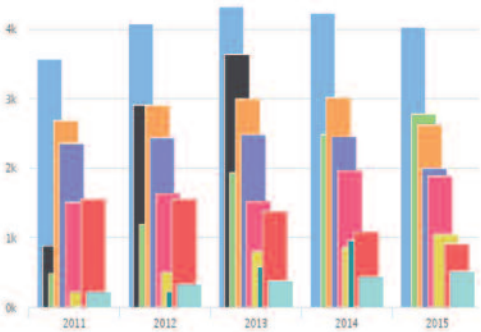
Elite also incorporates management details and contact information into the company capabilities profiles, and adds three apps that streamline research and provide instant analytics: TimeScape, Reconnaissance, and Label Comparison.

Elite equips you with the layered analytics and actionable insights needed to make strategic business decisions.

BUSINESS APPLICATIONS

- Research new therapeutic areas, and identify market gaps
- Uncover emerging science and evaluate new and promising technologies
- Target potential partners in a specific country or region, and screen potential licensing and investment opportunities
- Review comparable deals, acquisitions and financings
- Find and compare contract manufacturers and other outsourced services
- Assess the competitive landscape around an indication and research competitor pipelines
- Track generics and biosimilars, and identify Rx to OTC switch opportunities



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Serving: Medical Device, Life Science/Biomedical, Pharmaceutical, Veterinary & Dental industries; ISO 13485 & ISO 9001

Polymer Conversions, Inc. thrives on the challenge of providing full-service manufacturing operations for highly complex, precision plastic components using a fully Validated Process & Production Monitoring System. This system is networked to every injection molding machine and provides advanced real-time, shot-to-shot SPC data and archival of critical product specifications for every lot produced. Process limit reports mitigate risks at the earliest stages to reassure customers that they get consistent high-quality, precision products under the tightest, and most repeatable and reproducible processes. This superior scientific molding system means customers can be confident that at any time, Polymer can pull records to prove under what conditions and in which environments, each lot of their product was manufactured.

A cross-functional team representing an integration of expertise is capable of reviewing critical tolerances during R&D phases to determine the best overall design for manufacturability. This important step during product development helps to keep your overall project costs lower, a mission as critical to Polymer as it is to your own organization. Helping you find the right design and material properties early on will save you both time and money as your product moves from prototype to fully approved production.

The Polymer Conversions team believes in honesty, integrity, trust, transparency, and superior quality at a price that includes the cost of doing it right the first time. They are a reliable, flexible, technical, passionate, and dedicated team that truly cares about the end-users that rely on your products for critical-to-life situations.

Come and be a part of the Polymer Family.... They'd love to show you their ultra-clean facility and introduce you to their exceptional team who is ready and waiting to take on your next challenging innovation.

Don't forget to connect on LinkedIn for the latest updates from the Polymer Conversions and SILIKON Technologies teams!

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REVOX®
Sterilization Solutions
by Cantel Medical

ROOM TEMPERATURE STERILIZATION

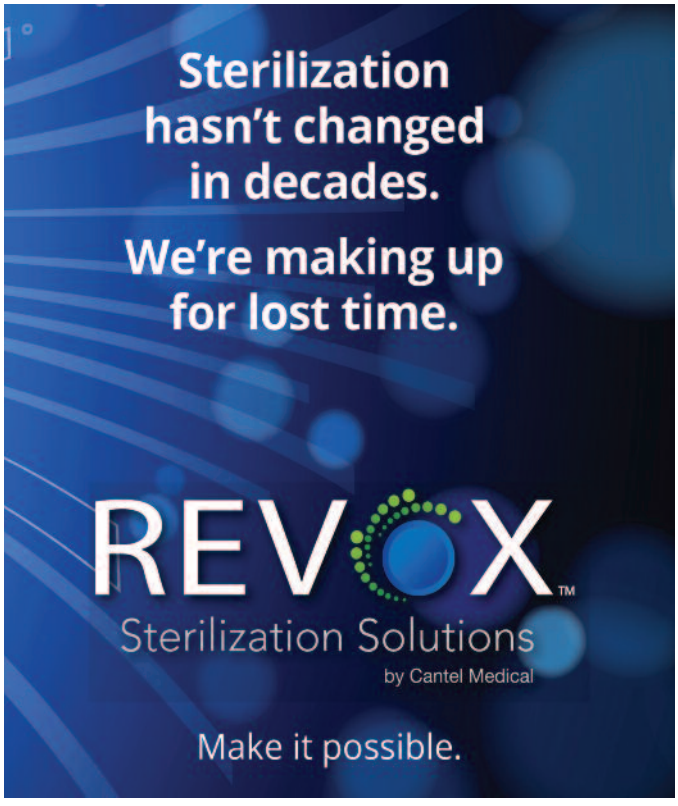
The REVOX® Sterilization Solutions process uses a patented, room-temperature vaporized peracetic acid (VPA) sterilant that achieves exceptionally low-chemical residuals and unsurpassed materials compatibility. The REVOX™ technology eliminates inefficiencies associated with pre-conditioning and lengthy post-sterilization wait times. This allows REVOX Sterilization to offer manufacturers a quick-turn, off-site sterilization service or cost-efficient on-site, in-line processing. In May 2014, a Class II implantable device was granted FDA clearance with the REVOX sterilization process. The REVOX innovation is backed by Cantel Medical, a company with over 35 years of infection prevention and control advancements structured under strict regulatory compliance standards.

SUPERIOR MATERIALS COMPATIBILITY

Until now, manufacturers have been limited by traditional sterilization methods that constrain their choices of materials and overall product design. Many materials that may otherwise be ideal for optimal product design simply are not suitable with common sterilization methods. REVOX changes that. With true room-temperature processing and demonstrated superior compatibility across a wider range of materials, manufacturers have more options to innovate more efficiently. Chemical and heat-sensitive materials that were once off-limits to innovative product development are now available. The REVOX sterilization process is compatible with over 100 materials, including biologics, implantables, electronics, pharmaceuticals such as combination devices, and more. You can now create the products that will demonstrate your true potential.

LEANER MANUFACTURING

The complete manufacturing stream should be exactly that: complete. Pulling components from the line for sterilization defeats the very purpose of having a production line. REVOX enables scalable in-line sterilization, which finally allows manufacturers to integrate sterilization into a lean manufacturing process. It speeds up production and gives manufacturers a substantial competitive edge. While some sterilization methods can take up to 44 cycles to sterilize two pallets of product, the REVOX 3000L machine takes just one. Think of it as JUST-IN-TIME™ sterilization. It's your time. Make the most of it.



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PYRAMID Laboratories, Inc. is a contract Aseptic Manufacturing and Analytical Services for Sterile Injectable Drugs. PYRAMID builds lasting partnerships with its clients and provides expertise in formulation and process development, aseptic filling for vials and syringes, as well as lyophilization applications, and supports early development through to commercial manufacturing. PYRAMID has established a reputation of exceptional performance, integrity, and quality. PYRAMID is committed to continuous improvement in quality, knowledge, and expertise, and we take pride in working with our partners to translate this commitment into safe products that will ultimately benefit the people who need it most – the patients.

TECHNICAL SERVICES

PYRAMID offers a wide array of services for all phase of drug development, including:

- Formulation & Process Development
- Lyophilized Product Formulation Development
- Lyophilization Cycle Development
- Clinical & Commercial Vial & Syringe Fill/Finish
- Clinical & Commercial Lyophilization Batches
- Analytical Quality Control Support

Formulation/Product Development

PYRAMID'S expertise in Formulation Development covers a wide range of products. The company assists clients through Product Development and Clinical phases to high-speed Commercial-scale production.

Lyophilization

PYRAMID has expertise in Lyophilization product and cycle development for a wide range of matrices. The facilities are equipped with a research and development laboratory-scale 36-sq-ft Stokes Freeze Dryer for clinical supplies, and a state-of-the-art 213-sq-ft Telstar Freeze Dryer for commercial scale batches. The company's freeze-dryers process vials in sizes from 2 mL to 20 mL.

Aseptic Filling

PYRAMID offers vial fill ranges from 0.5 mL to 20 mL with 100% weight check, and syringe fill ranges from 0.2 mL to 3 mL.

Analytical Services

PYRAMID's extensive Analytical Laboratory has the technical capability, quality, and capacity to perform a variety of analytical applications and has served the biopharmaceutical industries since 1988. The company has extensive expertise in:

- Analytical Method Development & Validation
- Validation for Stability Indicating Methods
- Long-Term & Accelerated Stability Studies
- Protein, Peptide, Oligonucleotide Characterization Assays

Storage & Distribution

PYRAMID has a 27,000-sq-ft facility for Labeling, Storage, and Distribution Services to store and distribute parenteral drug products across the globe during the entire clinical and commercial life cycle. PYRAMID's latest addition includes 27,600 cubic feet of monitored, alarmed validated chambers with environmental conditions for clinical and commercial drug product and API storage at ambient, refrigerated, frozen or ultra-low storage.

FACILITIES

PYRAMID Laboratories, Inc. is located in Costa Mesa, CA. Our facilities are housed in three buildings covering more than 70,000 sq ft. The combination of our manufacturing facilities and state-of-the-art laboratory allows PYRAMID to offer the pharmaceutical and biotech industry both analytical and manufacturing support capabilities. An intensive in-house Quality Assurance and Quality Control program is maintained to ensure clients receive high-quality products.

PYRAMID LABORATORIES, INC.
3598 Cadillac Avenue - Costa Mesa, CA 92626
T: (714) 435-9800 F: (714) 435-9585 Contact Person: Ellen Green, ellen@pyramidlabs.com
W: www.pyramidlabs.com PYRAMID Laboratories, Inc. is on LinkedIn

PYRAMID
Laboratories, Inc.

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- Formulation Development
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Headquartered in Billerica, MA, **Pion Inc.** supports the drug development industry with a suite of innovative instrumentation, assays, software, CRO laboratory, and lab equipment maintenance services (Benson, NC) for precision measurement of physical chemical properties, including:

- Ionization Constant - pK_a
- Lipophilicity - log P/log D
- FLUX
- Permeability
- BCS Screening
- MicroDissolution
- Lipophilicity
- USP Dissolution
- PAMPA
- Solubility

Founded in 1996 by Dr. Alex Avdeef, Pion Inc. has been a leading innovator in the use of parallel artificial membrane permeability assays (PAMPA), which determine the permeability of substances from a donor compartment through a lipid-infused artificial membrane into an acceptor compartment. Pion's patented innovations in this area include Gastrointestinal, Blood Brain Barrier, and Skin PAMPA models that offer drug developers a rugged, robust, and affordable means of screening, promising drug compounds for passive membrane permeability.

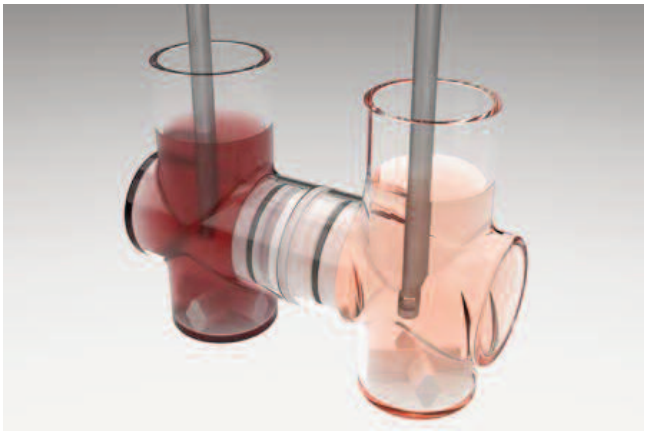
Pion is perhaps best known for its Rainbow fiber-optic monitoring system, which is used by all of the world's top 20 pharmaceutical companies for comprehensive, high-frequency capture of *in situ* UV dissolution data. The small-volume µDiss Profiler™ fiber-optic system supports small-scale dissolution experiments that enable end users to obtain comprehensive data while saving precious APIs and bio-relevant media.

Recently, Pion has leveraged its knowledge of PAMPA models and fiber optics to develop FLUX testing technology, which combines traditional dissolution testing with a repeatable method for assessing the absorption potential of APIs, API/ingredient combinations, or finished dosage products. The result is a single combined test that makes more reliable and realistic IVIVC (*in vitro-in vivo* correlation) testing and modeling possible.

Pion FLUX testing technology is available in two sizes: MicroFLUX testing, offered as an option on the µDiss Profiler system, is ideal for assessing early-stage APIs and unformulated combinations in small-volume tests of 20 ml or less. MacroFLUX testing is used with the Rainbow system and sized to evaluate the dissolution and absorption performance of finished dosage products in volumes of 500ml, 900ml, or 1l.

Pion's PULSE™ instrument offers a cost-effective solution for pK_a, log P/D, and solubility analysis. This potentiometric system, which is powered by Pion *Attain* and *Refine* software, offers both UV and autosampling options to meet a range of requirements and budgets.

The company's latest offering, Field Services, enables end users to outsource the maintenance, calibration, and repair of all leading brands of laboratory equipment to skilled Pion personnel.



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TERUMO
PHARMACEUTICAL SOLUTIONS

About Terumo

Terumo Pharmaceutical Solutions is one of the world's leading medical technology companies and operates in more than 160 nations. Terumo, founded in 1921, develops, manufactures, and distributes a broad range of world-class medical devices, including the supply of drug delivery/injection devices to the pharmaceutical industry.

Terumo Pharmaceutical Solutions

Terumo Pharmaceutical Solutions offers the pharmaceutical and biotechnology industry unique solutions in medical technology. In addition to offering our valued products, our specialized team also provides customized and dedicated solutions designed to meet your specific requirements.

Our Vision

Terumo believes that to produce medication without giving due consideration to the final drug delivery device is to miss the point of pharmaceutical development. In fact, it was this belief that led us to apply our long experience in medical technology for pharmaceutical purposes. Our aim is to ensure you can deliver your drugs safely, reliably, and uncontaminated, avoiding errors in medical practice while minimizing patient trauma and discomfort. We also strive to increase efficiency, reducing your total costs throughout the production process and product lifecycle.

Innovation

Innovation is part of Terumo's heritage. We created Japan's first precision clinical thermometer, single-use plastic syringes, and flexible blood bags, as well as the world's first hollow-fiber oxygenator. Many of our medical technologies have gone on to set new international standards and inspire further innovations. By focusing exclusively on medical technology from the beginning, we have developed a high degree of scientific expertise, technological know-how, and an in-depth understanding of medical practice. Our particular excellence in core areas allows us to make an invaluable contribution to the pharmaceutical industry.

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SHL GROUP

SHL is one of the world's largest solution providers in design, development, and manufacturing of advanced drug delivery systems. We work with leading biotechnology and pharmaceutical companies to develop drug delivery devices, including compact disposable auto injectors, reusable pen injectors, and complex inhaler systems. These devices use standard pre-filled syringes and cartridges, as well as novel primary containers.

SHL has always been investing significantly into R&D. The investment has especially intensified over the past 10 years, allowing us to enhance our broad pipeline of "next-generation" drug delivery devices. These include a range of disposable and reusable injectors with fixed or variable dosing, high dose accuracy, and the ability to accommodate high volumes and high viscosities. Developing these drug delivery devices in-house allows us to customize existing platforms in our pipeline or develop completely new bespoke devices based on the unique requirements of our customers. With locations in Taiwan, Sweden, and the US, our experienced engineers and designers develop product enhancements and breakthrough drug delivery solutions for clients globally.

As SHL is determined to provide the most comprehensive range of solutions and services, we maintain all key capabilities and processes in-house to ensure the best quality and time-to-market. SHL offers:

- Innovative device design based on customer/patient needs
- An advanced in-house tooling center for drug delivery devices
- An extensive range of moulding solutions
- Customized assembly and testing equipment
- Semi-automatic and fully automatic assembly solutions
- Analytical sciences responsible for full test method development, validation, and transfer
- Final assembly, labeling, and packaging services for drug delivery devices
- ISO13485- and FDA 21 CFR 820-compliant systems
- 510K clearance and compliance to medical device cGMPs
- A wide range of own patented solutions, significant licensing opportunities, and strong commitment to protecting customers' IP
- Proven track record of successful devices on the market
- Dedicated experienced professionals to ensure the success of your project
- Forward-looking initiatives exploring new technologies and future developments, including comprehensive connectivity offers

With over 3500 staff worldwide, our organization consists of several distinct group companies:

SHL Medical
Designs, develops and manufactures advanced drug delivery devices for leading pharmaceutical and biotech companies.

SHL Healthcare
Develops and manufactures equipment solutions for home, hospital, and long-term care use.

SHL Technologies
Provides contract manufacturing and engineering services for the production of complex medtech and industrial products.

SHL Pharma
Provides final assembly, labeling, and packaging services of drug delivery devices to the pharmaceutical and biotechnology industries.

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SHL GROUP

Connectivity Solutions

- ✓ Drug Delivery Devices
- ✓ Training and Instruction
- ✓ Supply Chain Tracking

UPM Pharmaceuticals® is a Bristol Tennessee-based contract development and manufacturing organization (CDMO) serving the pharmaceutical and biotechnology industries. UPM provides high-quality pharmaceutical drug development services that include formulation development, cGMP manufacturing and packaging, analytical method development, and testing from concept through commercialization.

UPM is characterized by its strict sense of quality, timeliness, sound scientific fundamentals, and affordability with which we complete all our projects. We focus on drug development and manufacturing for dosages with oral routes of administration in solid forms, such as capsules and tablets, and semi-solid creams and ointments.

Scientific Expertise — UPM's scientific team includes some of the industry's best analytical chemists, formulators, and manufacturing specialists. Our experienced scientists provide innovative ideas and guidance to address our clients' unique product development challenges, such as low dose content uniformity, high dose compressibility, controlled drug release rates, and experimental designs for limited API availability.

Rapid and Responsive Turnaround — Our scientists and managers utilize daily planning meetings and a master scheduling process to ensure that every project will be completed on time, every time.

Quality Assurance Documentation — Our highly experienced quality assurance personnel implement complete cGMP quality systems that support formulation development, cGMP batch manufacturing, and analytical testing.

TABLETS
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- Controlled humidity suite
- DEA controlled substances (CII-CV)
- Clinical and commercial scale

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- Range of 150-100,000 capsules per hour
- Liquid fill encapsulation

CREAMS & OINTMENTS
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- Automated packaging lines for tubes and jars

DEA Licensed / FDA Inspected

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Acute Coronary Syndrome – Global Drug Forecast and Market Analysis to 2025

GlobalData's Acute Coronary Syndrome (ACS) report gives a comprehensive evaluation of current treatment paradigms. As well as a ten-year market forecast, the report also discusses key unmet clinical needs in the ACS space, and highlights important challenges and opportunities over the next ten years.

Get a detailed picture of the ACS market:

- The main driver of growth will be the increase in use and physician confidence in the PCSK9 inhibitor class
- ETC-1002 will also be a major contributor, and will compete for patient share in the statin-intolerant ACS population
- The major barrier will be generic erosion of the key antiplatelet therapies Brilinta and Effient – although both will gain significant sales momentum prior to patent expiry
- Market dynamics will shift away from the historical strategy of developing antithrombotic therapies, and towards solving the atherosclerotic burden
- Key opportunities lie in the development of optimal agents for secondary prevention, by controlling lipid levels and repairing the damaged myocardium post myocardial infarction

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YOUR PARTNER IN ASEPTIC FILLING

Vetter is a leading contract development and manufacturing organization (CDMO) that specializes in the aseptic filling of syringes, cartridges and vials. Vetter holds numerous patents and has extensive experience with biologics and other complex compounds, including monoclonal antibodies, peptides, interferons, and vaccines. More than 70% of Vetter's active projects are biologics, and Vetter currently manufactures 5 of the world's top 10.

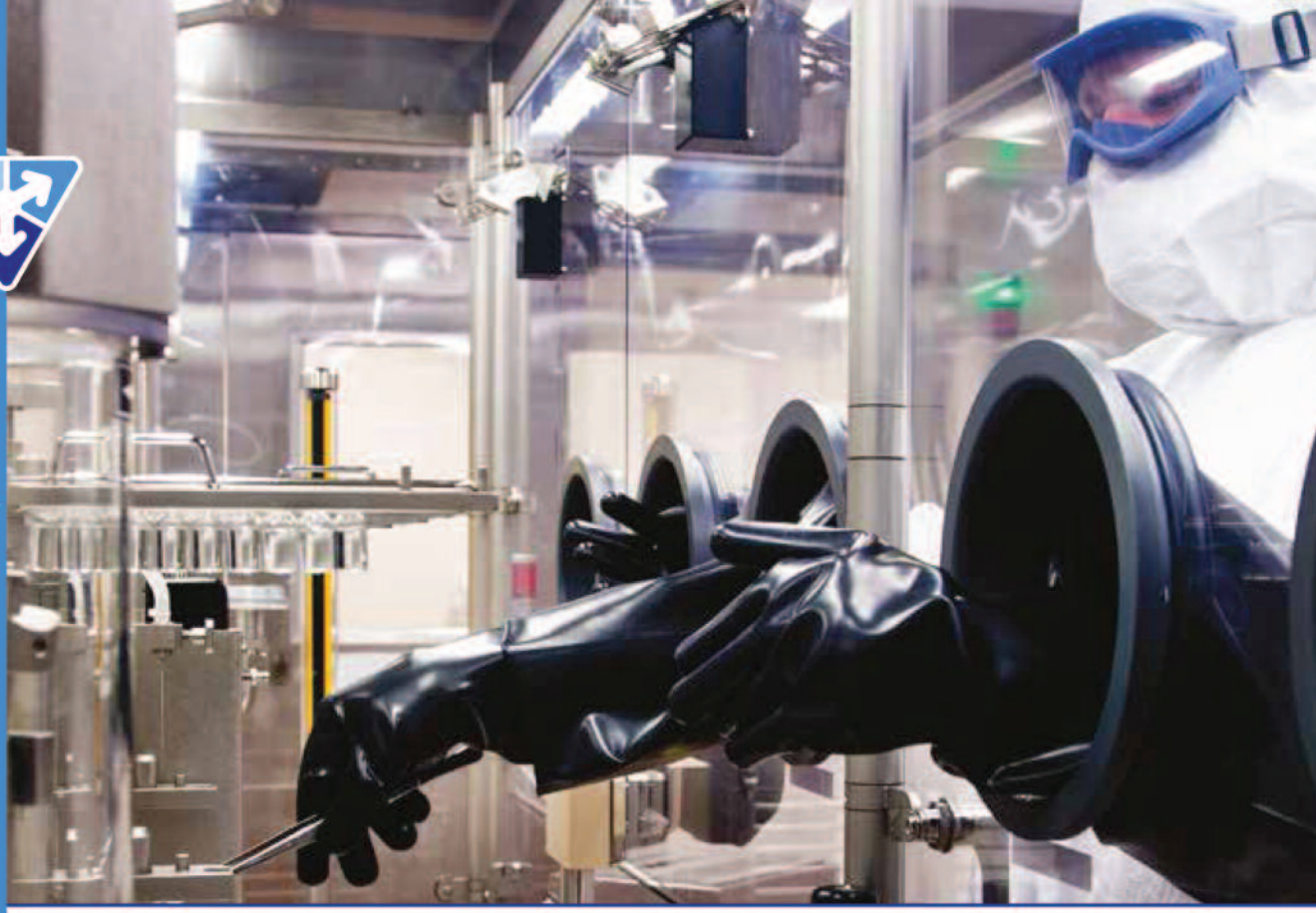
Collaborating with the top 10 (bio-)pharmaceutical companies worldwide, Vetter supports products from preclinical development through global market supply. Through its US and European facilities, Vetter Development Service provides state-of-the-art support for early stage products, with seamless transfer at Phase III to Vetter Commercial Manufacturing for large-scale production. We offer state-of-the-art technology and innovative processes to promote product quality and maximize API yield.

VETTER AT A GLANCE

- Headquarters in Ravensburg, Germany
- Additional clinical development facility in Chicago, US
- A Representative offi ce for Asia Pacific in Singapore and a subsidiary in Japan
- Approximately 3,900 employees
- Worldwide specialist in the aseptic production of prefilled drug delivery systems
- Global experience and expertise with regulatory authorities including FDA, EMA, PMDA (Japan), and RP (Germany)
- Approx. 50 customer products with FDA approval

CONTACT US

Visit www.vetter-pharma.com or contact us at info@vetter-pharma.com for more information.



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West Pharmaceutical Services, Inc.

Committed to quality, collaboration, service and innovation

West is a leading global manufacturer in the design and production of technologically advanced, high quality, integrated containment and delivery systems for injectable medicines. We are a trusted partner to the world's top pharmaceutical and biotechnology companies—working by their side to improve patient health.

West Offers Proprietary Packaging, Containment and Drug Delivery Products

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- **Self-injection systems:** innovative, patient-centric technologies that are easy to use and can be combined with connected health technologies that have the potential to increase adherence
- **Containment and delivery systems:** including Daikyo Crystal Zenith®—a high performance polymer alternative to glass that can meet the challenges of sensitive biologics

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West contract manufacturing harnesses a powerful combination of innovation, technology, infrastructure and expertise to serve the pharmaceutical, medical and consumer industries. Along with more than 40 years of experience, we bring customers quality, safety and reliability in injection molding, contract assembly and finished packaging from our eight locations throughout North America and Europe.

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- **7,100 global employees**
- **Founded in 1923**
- **2015 sales: $1.4 billion**
- **West products used on a daily basis: approximately 110 million units***

*Based on 2015 annual sales.

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Protect Your Brand™ is a unique offering designed to support pharma-biotech companies pursuing a dual sourcing strategy. Under this program, Alcami will support tech transfer and validation of products in advance of potential manufacturing needs without any long-term commitment or minimum annual volume. It's that simple. Protect Your Brand offers three distinct dual supply solutions to prevent disruptions from occurring at the earliest during clinical supply through to post-approval commercial production. This service can be used for drug substance, drug product, and for clinical supplies, launch quantities, and commercial supply. Protect Your Brand allows you to determine the ideal State of Alcami Readiness™ needed for your product. Responding quickly allows Alcami to minimize the effects of a supply disruption, helping prevent shortages and delays. Alcami can be ready quickly to bridge unexpected gaps in your critical supply needs. For more information, visit Alcami at **www.alcaminow.com.**

CDMO Services

ALTHEA

THE POWER TO MAKE

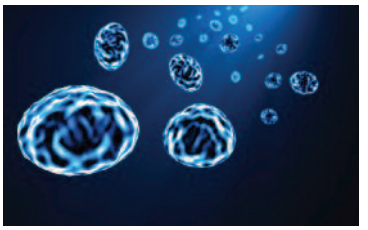
Althea is a fully integrated, contract development and manufacturing organization providing clinical and commercial product development services. Althea offers cGMP drug product filling in both vials and syringes, and production of microbial-derived recombinant proteins and plasmid DNA. In conjunction with these manufacturing operations, Althea offers comprehensive development services, including upstream and downstream process development, analytical development, lyophilization cycle, complex formulation, product release and ICH-compliant stability testing. In addition, Althea offers a proprietary formulation technology platform, Crystalomics®, and an innovative recombinant protein expression technology called Corynex® technology. Althea is the manufacturing partner that delivers the relentless dedication and support our clients need. For more information, visit Althea at **www.altheacmo.com**.

Innovative Logisitcs Management

AmerisourceBergen®

AmerisourceBergen is a leading global healthcare solutions company, helping both manufacturers and providers improve patient access and enhance patient care. Our businesses have been a key component in the commercialization of virtually every successful specialty product in the past decade, including more than 100 orphan and rare disease products. We understand the unique challenges your patients face as well as the complex decisions required at each stage of the product life cycle. Our clinical trial refrigeration inventory management technology, CubixxCT® automates processes to reduce costs, errors, time, and drug accountability workloads. Product temperature is tracked in real-time, for complete visibility and transparency, 365/24/7. This portable in-home solution enhances the patient's clinical trial experience and allows easy access to product, while sponsors, CROs, and study teams retain complete control and oversight at every location and for every product stored in CubixxCT®. For more information, visit AmerisourceBergen at **www.ItTakesAmerisourceBergen.com**.

Nanoparticle Formulations



Ascendia Pharmaceuticals is a contract development and manufacturing (CDMO) company offering services for formulation development of poorly soluble drugs and other challenging development programs. Our formulation options include nanoemulsions, amorphous solid dispersions, nanoparticles, liposomes, and oral controlled release. These technologies are suitable for oral, topical, or injectable dosage forms. NanoSol is our technology for production of nanoparticle formulations. Ascendia has the capability to make nanoparticles from native drug crystals using ball milling, or lipid-based nanoparticle composites for lipophilic drugs. When the nanoparticle is delivered to the body there is greater surface area for dissolution, and by using enhancers in the formulation higher bioavailability can be more readily achieved. Ascendia can optimize nanoparticle formulations and produce clinical trial materials for first-in-man studies. For more information, contact Ascendia at (732) 640-0058 or visit **www.ascendiapharma.com**.

Leading CDMO

AVISTA PHARMA

Avista Pharma Solutions is a premier contract testing, development, and manufacturing organization that provides a broad range of leading services from discovery, early stage API and Drug Product development and cGMP manufacturing to stand-alone analytical and microbiology testing support. We are your experienced, capable, dependable partner, serving pharmaceutical, animal health, and medical device clients from over 200,000 square feet of laboratory and manufacturing space across three locations (Agawam, MA; Durham, NC; and Longmont, CO). We support your development program from Nomination to IND/Phase I to Proof-of-Concept/Phase II/Phase III. We have the FLEXIBILITY and CAPACITY to meet your project's FAST TIMELINES. For more information, contact Avista Pharma Solutions at (866) 459-4600 or visit **www.avistapharma.com.**

Product Development & CMC Services

AVOMEEN ANALYTICAL SERVICES

Avomeen - From API Synthesis to after-market support, our experienced chemists support all segments of your drug development pipeline. As a full-service laboratory, we provide customized services that aid pharmaceutical researches, developers, and manufactures. You'll be in good hands with our reliance on a Quality by Design (QBD) approach and rejection of the typical "list price testing." We recognize that every project is unique, which drives us to spend the time to find out the true nature of our clients' needs and develop a personalized plan just for you. Our multi-disciplinary scientists have years of experience with multiple dosage forms, including transdermal delivery systems, ointments, tablets, capsules, films, polymers, coatings, and drug-device combination products. Contact us today for a Complementary Initial Consultation with one of our PhD Chemists. For more information, contact Avomeen at (800) 930-5450 or scientist@avomeen.com, or visit **www.avomeen.com/pharma.**

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BASF creates chemistry for a sustainable future offering intelligent solutions to the pharmaceutical industry. With our expertise in polymer chemistry, R&D-capabilities, and commitment to developing excipients, BASF creates solutions for Instant & Modified Release, Solubilization, Softgels, Skin Delivery, and Biologic applications. We also are a leading supplier of selected APIs, such as ibuprofen and omega-3. Our team of experienced industry specialists are here to support you in developing effective, reliable solutions to the formulation challenges you face today and tomorrow. For more information, contact BASF at (800) 469-7541 or visit **www.pharma.basf.com**.

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BioScreen Testing Services, Inc. (est. 1985, FDA registered, ISO 9001:2008 certified), headquartered in Los Angeles, CA, offers a wide range of testing services in Analytical Chemistry, Microbiology, and Human Clinical Trials . Additionally, the company offers an array of in vitro toxicological tests and consulting services. BioScreen's two Clinical sites (located in Phoenix, AZ, and Los Angeles) have one of the largest and most ethnically diverse subject databases in the industry (including Asian subjects). BioScreen's full-service chemistry lab is also the industry leader in heavy metal testing, boasting multiple ICP-OES, and ICP-MS instruments. Our customer service staff is friendly, helpful, and ready to assist you, and we provide routine quotes within 24 hours. For more information, visit BioScreen Testing at **www.bioscreen.com.**

Innovative Dosage Forms

Capsugel designs, develops, and manufactures a wide range of innovative dosage forms for the biopharmaceutical and consumer health & nutrition industries. Our unique combination of science, engineering, formulation, and capsule expertise enables our customers to optimize the bioavailability, targeted delivery, and overall performance of their products. We partner with more than 4,000 customers in over 100 countries to create novel, high-quality, and customized solutions that align with our customers' evolving needs and benefit patients and consumers. For more information, visit **www.capsugel.com.**

Platform Technology

Captisol is a patent-protected, chemically modified cyclodextrin with a structure designed to optimize the solubility and stability of drugs. Captisol was invented and initially developed by scientists in the laboratories of Dr. Valentino Stella at the University of Kansas' Higuchi Biosciences Center for specific use in drug development and formulation. This unique technology has enabled 8 FDA-approved products, including Onyx Pharmaceuticals' Kyprolis®, Baxter International's Nexterone®, and Merck's NOXAFIL IV. There are more than 30 Captisol-enabled products currently in clinical development. For more information, visit Captisol at **www.captisol.com.**

OptiForm® Solution Suite

Catalent's OptiForm® Solution Suite was launched in 2015, and combines both predictive and high throughput screening technologies to identify the most stable and efficient drug form for small molecules. By matching the best drug delivery technologies to each developmental molecule, optimal preclinical PK materials can be delivered in just twelve weeks. OptiForm Solution Suite Bio extends the rapid screening technology platform to include macromolecules, and the identification of suitable non-invasive methods of drug delivery for biological drug products. Expanding the scope to encompass macromolecules, OptiForm Solution Suite Bio employs Catalent's OptiGel™ Bio and Zydis® Bio advanced formulation technologies, and uses a parallel screening model, based on rigorous science and best-in-class formulation expertise, to deliver in vivo study material in as little as three weeks. For more information, contact Catalent Pharma Solutions at (888) SOLUTION or visit **www.catalent.com.**

Full-Service CDMO

CordenPharma is your full-service CDMO partner in the Contract Development & Manufacturing of APIs, Drug Products, and associated Packaging Services organized under 5 technology platforms: Peptides, Lipids & Carbohydrates, Injectables, Highly Potent & Oncology, Small Molecules, and Antibiotics. With multiple cGMP manufacturing facilities across Europe and the US, CordenPharma experts translate your complex ideas into high-value products at any stage of development. CordenPharma provides proprietary peptide, lipid, carbohydrate, and oligonucleotide technologies for cGMP-compliant products and services. We additionally specialize in the manufacturing and containment of highly potent peptide APIs (with exposure limits as low as 1 ng/m^3), highly potent formulations (solid forms), cephalosporins & penicillins (oral & sterile), oncology drug products (oral & sterile), and packaging. Visit CordenPharma at **www.cordenpharma.com.**

Super Refined™ Excipients

CRODA

Croda manufactures a complete range of high purity excipients and delivery aids, offering superior quality for the global pharmaceutical market. These excipients are ideal for multiple dosage forms, including topical, parenteral, oral, and ophthalmic formulations as well as advanced delivery systems. Croda's Super Refined™ excipients go through a proprietary process to remove the polar and oxidative impurities that can cause performance and stability issues. These excipients are ideal for use when working with sensitive drug actives, helping to maximize the stability and overall performance of the drug product. Excipients in the Super Refined range include PEGs, polysorbates, oils, and triglycerides, propylene glycol, castor oil, and a range of topical penetration enhancers, such as oleic acid and dimethyl isosorbide. For more information, contact Croda at (732) 417-0800 or visit **www.crodahealthcare.com**.

On Body Delivery System

Enable Injections' on body delivery system (OBDS) delivers high-volume, often viscous drugs subcutaneously for patients to conveniently and discreetly inject at home, work, or on the move. The design is based upon over 12 years of research in minimizing injection pain with a strong emphasis on the end-user and Human Factors. The platform consists of a single injector up to 5-ml, 10-ml, 20-ml, 30-ml, 40-ml, 50-ml capacity - and associated transfer system. One of the three transfer systems (Syringe, Vial, or Fully Automated Reconstitution) is combined with each injector to provide the user with a simple disposable package. This package transfers the drug from the original container closure to the injector in a few intuitive steps. For more information, visit Enable Injections at **www.enableinjections.com**.

Automated Delivery System

Enhancing patient lifestyle I Extending product lifecycle

OmniPod® DELIVERY SYSTEM

Insulet Corporation is an innovative medical device company based in Billerica, Massachusetts. Insulet designs and manufactures the OmniPod® Delivery System, an intelligent wearable subcutaneous pod used in a variety of therapeutic areas. This automated drug delivery system helps offer improved adherence, outcomes and differentiation throughout a drug's lifecycle. Equipped with a soft delivery cannula for a virtually painless experience and adhesive backing for extended wear, OmniPod is the on-body device that allows patients to live life uninterrupted. For more information, contact Insulet at (978) 600-7011or visit **www.omnipoddelivery.com.**

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EG-GILERO is your single-source, trusted partner for design, development, and contract manufacturing within the medical device, drug delivery, and primary pharmaceutical packaging markets. Acting as a seamless extension of your own internal resources, we accelerate speed to market of innovative devices from concept straight through commercialization. Design & Development is in our DNA. Our experienced engineering team provides a full suite of design and development services for your medical device and drug delivery device product development projects. Beginning with the end user in mind, EG-GILERO conducts clinical site user research, novel concept development, smart rapid prototyping, detailed engineering, and IP management. By adhering to strict design controls and our ISO 13485 certified quality management system (QMS), EG-GILERO integrates human factors engineering (HE75) and design for manufacturability (DFM) throughout the entire development process. For more information, contact EG-GILERO at (844) 344-5376 or visit **www.eg-gilero.com.**

Formulation Development

Compritol® 888 ATO is an inert, GRAS, tasteless/odorless, hydrophobic white powder used in formulation of solid oral dosage forms. Listed in the IID database as Glyceryl Behenate, Compritol is referenced in many marketed drugs – including pediatrics. Applications include: hydrophobic coating for taste masking of API; sustained- or delayed-release matrices by direct compression, capsule molding, or formation of granules by spray congealing or melt extrusion; preparation of solid lipid-nanoparticles; and tablet lubricant for API that are sensitive to magnesium salts. For more information, contact Gattefossé at info@gattefossecorp.com or visit **www.gattefossecorp.com.**

Formulation Development

LATITUDE Pharmaceuticals, Inc.

Latitude Pharmaceuticals, Inc. extends its reputation each day among drug developers as the go-to formulation group for problematic APIs. Whether the need is for a quick PK/Tox formulation or a complete IND-ready formulation development program that covers analytical, manufacturing process, and new IP protection, Latitude draws on its extensive experience and technical expertise to complete each project rapidly, efficiently, and cost effectively. We have the experienced personnel and an extensive range of analytical and manufacturing platforms to develop prototypes of nearly every kind of injectable, oral, topical, inhalation, and ophthalmic human and veterinary formulation – both simple and complex. If your API is insoluble, poorly bioavailable, irritating, physically and/or chemically unstable, tastes bad, requires a special PK or tissue distribution, or requires a proprietary, complex, or generic formulation, contact Latitude at (858) 546-0924, ext 118, or visit **www.latitudepharma.com.**

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Get Noticed. Get Funded. Grow Faster. When you need to connect with investors, business partners, and regulatory agencies, LifeSciencePR can make that happen. Our integrated communication strategies and well-established industry contacts will help your life science company achieve its short- and long-term corporate objectives. We work seamlessly with your senior management team to develop the most effective communication initiatives to reach your prospective investors and partners. Our experienced staff knows what it takes to break through with your breakthroughs, powering your engine in your continued drive toward your success. LifeSciencePR will get you there smarter, faster, and easier than any other marketing and communications firm in the industry. For more information, contact LifeSciencePR at (800) 724-2372 or visit **www.LifeSciencePR.net.**

Development/Clinical Trial Manufacturing

Lyophilization Technology, Inc. (LTI) provides Development and Clinical Trial Material Manufacturing services to biotechnology and pharmaceutical clients spanning virtual, small, and large multi-national companies. Experience with a diverse range of products, including small molecules, cytotoxics, biologics, highly potent compounds, vaccines, medical devices, and diagnostic agents, LTI has developed formulations, manufacturing processes and prepared material for clinical trials. The operation is able to process a broad range of container closures, including 2-mL to 160-mL vials, 1-mL to 50-mL cartridges/syringes, bulk trays, and unique devices for batch sizes up to 75 L. Services consist of thermal analysis, product design, formulation development, process design/refinement, product characterization, preparation of preclinical through Phase II clinical supplies, along with technical consultation, technology transfer, validation, product/process evaluation, troubleshooting, streamlining operations, auditing, and training. For more information, contact LTI at (215) 396-8373, inquiry@lyo-t.com or visit **www.lyotechnology.com.**

Stability Storage Facility

Metrics Contract Services is investing $3.5 million in a 15,000-square-foot stability storage expansion that will triple its current capacity. Scheduled to open spring 2017, the facility will feature large, walk-in chambers with state-of-the-art controls. The investment is being driven by the growth of clients' registration batch stability programs in support of various international markets. The company's expanding portfolio of clients who have successfully brought drug products to commercialization also requires additional stability storage support. As a full-service, global drug development and manufacturing organization, Metrics is committed to ensuring we adequately support client's needs throughout their product's life cycle. Our goal is to become the oral-dose "concept to commercialization" CDMO of choice for pharma companies, and our larger stability storage capacity represents part of that commitment to meet client needs. For more information, visit Metrics Contract Services at **www.metricscontractservices.com.**

Highly Lubricious Material

Quniton™ has performance capabilities uniquely designed to improve and withstand Medical and Pharmaceutical application needs. Formulated to have a low coefficient of friction, it resists bonding or sticking to a wide range of materials and diversifying interface capability. Enhancing product lifespan, Quniton™ possesses non-reactive properties that ensure consistent surface-to-surface contact over time, retaining chemical and thermal stability. Industry applications include: MEDICAL & PHARMA - Plunger and Caps, Valves, Pumps, Seals, Syringe Plugs, Vial Seals, Catheters, Connections, and Diaphragms. For more information, visit Minnesota Rubber at (952) 927-1400 or visit **www.mnrubber.com.**

Oxygen Absorbers

Need a solution for complex drug substance or drug product stability requirements? **Multisorb Technologies'** StabilOx® oxygen absorbers are a unique product that manages moisture and oxygen inside your package to respond to ever-changing conditions within the packaged environment. By reducing oxygen concentrations while managing moisture to the required level, StabilOx works to meet your drug's chemical and physical stability requirements. This helps ensure drug stability and performance, thereby extending product shelf-life, increasing product quality and ultimately, your revenues. Available in a variety of formats and sizes including packets, canisters, and adhesive labels, StabilOx can be used in virtually any packaging presentation. For more information, visit Multisorb Technologies at **www.multisorb.com.**

Drug Delivery Solutions

With over 1,500 people and 4 plants across two continents, Nemera is a world leader in the design, development and manufacturing of drug delivery solutions for the pharmaceutical, biotechnology, and generics industries. Nemera leverages decades of experience in the devices sector, from full solution development to pure contract manufacturing, through customized solutions. Nemera's expertise covers several modes of delivery: Ophthalmic (multidose, preservative-free eyedroppers), Nasal, Buccal, Auricular (pumps, valves, and actuators for sprays), Dermal & Transdermal (airless and atmospheric dispensers), Parenteral (auto-injectors, pens, safety devices, and implanters), and Pulmonary (pMDIs, DPIs). Over 5 million diabetics and 10 million asthmatics use every day the devices manufactured by Nemera. For more information, contact Nemera at information@nemera.net or visit **www.nemera.net.**

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What do you *really* know about end users of drug delivery technologies?

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Our expert healthcare analysts:

- Identify growth challenges and optimal growth strategies
- Evaluate each strategy to identify those producing the best ROI
- Develop client-tailored, effective implementation strategies

For more information on how to find growth opportunities in the drug delivery market, please contact Mireya Espinoza at mireya.espinoza@frost.com or **210-247-3870**.

www.frost.com

Device Training Platforms

Noble develops device-comparable injection and respiratory training platforms to provide biopharmaceutical companies improvements in patient medication adherence. These training platforms are built to brand specifications and are available as off-the-shelf and customized solutions, including proprietary technologies. Noble's offerings range from mechanical training devices to smart error-correcting training platforms, which replicate a brand's shape, design and tactile feedback, operational forces, and steps needed to administer the drug. These devices are designed to mimic actual delivery devices while being a low-cost reusable solution to safely and effectively onboard users. Benefits of patients using a device-comparable trainer before using an actual drug delivery device include users becoming familiar with a brand's device design, functionality, and ergonomics while learning correct administration technique. Companies providing reusable, device-comparable training products will be well positioned for competitive differentiation through improved patient satisfaction, adherence, and outcomes. For more information, contact Noble at (888) 933-5646 or visit **www.gonoble.com.**

Patheon OneSource™

Take months off the development timelines of your large and small molecule discoveries. With **Patheon OneSource™** you can combine your drug substance and drug product development and manufacturing into a single customized solution to simplify your supply chain and accelerate your discovery to proof of concept. You'll be able to develop small molecules 8-12 weeks faster than the industry-standard 15 months, and large molecules 14-20 weeks faster. In the pharmaceuticals industry, speed is important but consistent high quality is a must. Your project will be carefully monitored by our global quality management system. This will ensure that each and every dose is equally compliant, safe and effective. It is a proven approach that prevents costly disruptions, guides continuous improvement and has earned Patheon an unmatched track record for quality. For more information, visit Patheon at **www.patheon.com/onesource.**

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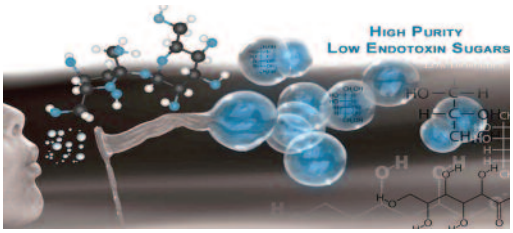

Pfanstiehl is a leading cGMP manufacturer of parenteral grade excipients and highly potent APIs. Pfanstiehl develops and manufactures high-purity, low-endotoxin (HPLE) carbohydrates such as trehalose, sucrose, mannitol, galactose, and mannose utilized as injectable excipients for the stabilization of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

Global Data & Analytics

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

Physico Chemical Property Measurement

Accelerate your drug development process with Pion's innovative instruments and comprehensive services. Our µDiss in situ monitoring systems allows for comprehensive analysis of pharmaceutical actives in complex matrices. The system runs parallel small-volume dissolution experiments, utilizing less API and biorelevant media. NEW µFlux and MacroFLUX systems are in vitro pharmacokinetic instruments for simultaneously measurement of dissolution and permeation. PULSE is a potentiometric and UV platform to allow for the determination of traditional parameters like pKa and log P/D. Contract Research Lab provides superior data analysis and interpretation in physico chemical property measurement. NEW Field Services-Provide equipment maintenance, calibration, and repair of all leading brands. See how our expertise in physico chemical property measurement can benefit you. For more information, contact Pion at sales@pion-inc.com or visit **www.pion-inc.com.**

Medical Contract Manufacturer

Polymer Conversions, Inc. is a Full-Service Medical Contract Manufacturer with in-house specialties in: Design – Engineering – Tooling – Validations – Clean Room Manufacturing – Assembly – Decorating - Packaging. FDA Registered – ISO 13485 – Class 7 & 8 Clean Room Operations - cGMP Compliant. Companies partner with Polymer to get advanced engineering and design assistance as well as to outsource complex, thermoplastic injection molding and value-added operations for Life Science, Medical Device, Pharmaceutical, and Biomedical products. They also offer Precision Silicone components from sister company, SILIKON Technologies, which specializes in Class 8 Clean Room Silicone Injection Molding, Assembly & Packaging. From start-up to global OEM, Polymer & SILIKON love the challenge of solving difficult issues for partners that create critical-to-life product innovations. For more information, contact Polymer Conversions at (716) 662-8550 or visit: **www.polymerconversions.com.**

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REVOX® Sterilization uses a patented, room-temperature peracetic acid (PAA) vaporized sterilant that achieves exceptionally low chemical residuals and unsurpassed materials compatibility. With superior compatibility across a wider range of materials, engineers have more options to create products more efficiently. Companies can now create the products that will demonstrate their true potential. The REVOX™ technology eliminates inefficiencies associated with pre-conditioning and lengthy post sterilization wait times. This allows REVOX Sterilization to offer manufacturers a quick-turn, off-site sterilization service or cost efficient on-site, in-line processing. In May 2014, a Class II implantable device was granted FDA clearance with the REVOX sterilization process. The REVOX innovation is backed by a company with over 35 years of infection prevention and control advancements structured under strict regulatory compliance standards. For more information, visit REVOX at **www.revoxsterilization.com.**

Advanced Delivery Devices

SHL is the world's largest privately owned designer, developer, and manufacturer of advanced drug delivery devices, such as auto-injectors and pen injectors. We have over 2,600 staff globally, with our primary design centers located in the USA and Sweden and manufacturing centers located in Asia. SHL supplies auto-injectors, pen injectors, and inhaler systems to global pharmaceutical and biotech companies. Significant investment in R&D has enhanced our broad pipeline of "next-generation" drug delivery systems. These innovative devices include a range of disposable and reusable injectors with fixed or variable dosing, enhanced precision, and the ability to accommodate high viscosities. For more information, contact SHL Group at info@shl-group.com or visit **www.shl-group.com.**

Advanced Medical Technology

Terumo is one of the world's leading medical technology companies and operates in more than 160 nations. Terumo, founded in 1921, develops, manufactures and distributes a broad range of world-class medical devices including the supply of drug delivery/injection devices to the pharmaceutical industry. Terumo Pharmaceutical Solutions offers the pharmaceutical and biotechnology industry unique solutions in medical technology. In addition to offering our valued products, our specialized team also provides customized and dedicated solutions designed to meet your specific requirements. For more information, visit **www.terumo-ps.com.**

Development Services

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November/December 2016 Advertiser Index

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a. Total # of copies	15,558	15,775
b. Legitimate Paid and/or Requested Dist.		
1. Individual Paid/Requested Subscriptions	15,000	15,000
2. Copies Req. by Employers for Dist. to Employees	0	0
3. Sales through dealers and carriers, Street Vendors, Counter Sales and other	0	0
4. Req. copies dist. by other mail classes through USPS	73	76
c. Total paid and/or req. circulation	15, 073	15,076
1. Outside County Nonreq. copies	0	0
2. In County Nonreq. copies stated on PS Form 3541	0	0
3. Nonreq. copies distributed through USPS	0	0
4. Nonreq. copies distributed outside the mail	385	524
e. Total nonreq. distribution	385	524
f. Total Distribution	15,458	15,600
g. copies not distributed	100	175
h. Total	15,558	15,775
i. Percent paid and/or requested circulation	97%	96%

16. Publication of Statement of Ownership for a requester publication is printed in the November/December 2016 issue

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External Delivery

P.U.M.P. IT UP

By: John A. Bermingham

John A. Bermingham is former Executive Vice President & COO of 1st Light Energy & Conservation Lighting, Inc. and former Co-President and COO of AgraTech, a biotech enterprise. He was also President & CEO of Cord Crafts, LLC; President & CEO of Alco Consumer Products, Inc., Lang Holdings, Inc., and President, Chairman, and CEO of Ampad, all of which he turned around and successfully sold. With more than 20 years of turnaround experience, he also held the positions of Chairman, President, and CEO of Centis, Inc., Smith Corona, Corporation, and Rolodex Corporation as well as turning around several business units of AT&T Consumer Products Group and served as the EVP of the Electronics Group, and President of the Magnetic Products Group, Sony Corporation of America.

The acronym P.U.M.P in this column stands for Portland – Upper Mount Bethel Food Pantry. P.U.M.P is a not for profit 501(c)3 organization. Portland and Upper Mount Bethel are two townships in the Slate Belt area in Northeast Pennsylvania. The townships are located adjacent to each other and are between Easton, PA, and Allentown, PA, in the beautiful Pocono mountains.

Let me first ask a question. Have you ever been really really hungry? I don't mean the hunger you experience in the morning or just before dinner. I'm talking about major league hunger. I had that experience only once in my life, and it was while I was in the Army stationed in South Korea just south of the DMZ. We ran out of food while out in the field on a practice missile shoot and did not get a resupply for almost 2 days. I didn't like that very much, and talk about being crabby! The point is, in this country, no one should have to experience that pain, especially children or the elderly.

The P.U.M.P food pantry is led by Sherman LaBarre as Chairman of the Board and is supported by several key people to include Skip Skinner whose name and contact information are at the bottom of the advertisement. Mr. LaBarre leads a group of volunteers who, every Monday, distribute the food collected the previous week from grocery stores and churches. Mr. LaBarre's late daughter, Sherma, started the food pantry 20 years ago in a room in a local church essentially on her own. Today, the P.U.M.P Food Pantry is her legacy and continues on under her father's leadership.

Currently, the P.U.M.P food pantry feeds more than 400 families and is continuing to grow. Growth means higher overhead costs. Higher overhead costs mean a greater need for food and financial donations. Because of this organization's rapid growth, it was forced to lease a larger facility that increased its monthly triple net lease payments; the "past their prime time" freezers holding the food donations are working overtime and need to be replaced; the refrigerator truck used for picking up food from donors has finally given up and must be replaced.

In keeping up with the spirit and true meaning of the upcoming holiday season, Drug Development & Delivery's founders (Publisher Ralph Vitaro and Executive Director Dan Marino) have generously donated money, advertising, and this editorial space to remind its readers to step back every so often and remember there are people in need right here in this very country. So I am asking all of you to please support P.U.M.P. Hunger does not recognize state borders, so, even though you or your company are not located in Pennsylvania, your personal or corporate donation is still greatly appreciated and will help tremendously. Call us today! ◆

Please keep in mind that all donations whether company or personal, are tax deductible being that P.U.M.P is a not for profit 501(c)3 organization.

PORTLAND-UPPER MOUNT BETHEL FOOD PANTRY, INC.
P.O. BOX 69 (mailing address)
111 State Street (physical address)
Portland, PA 18351

Chairman of the Board
Sherman LaBarre (570) 656-2967

Volunteers
Skip Skinner (610) 216-9800
John Bermingham (973) 452-5102

TOGETHER, WE CAN HELP.

Even in a first world country like the United States, people, especially children, wake up hungry and go to bed hungry.

Portland-Upper Mount Bethel Food Pantry, otherwise known as **PUMP**, is a not-for-profit 501(c)3 organization, who for the past 22 years has been fighting hunger daily. The organization began in a local church with a few volunteers and has now grown to supply food to over 400 families.

While we are currently supported by local churches and food stores, in order to meet the needs of a growing population of families in need, PUMP is reaching out to you to help us meet our growing overhead costs. A company or personal donation would be highly welcomed.

Also, because we are a not-for-profit 501(c)3 organization, your donation is tax-deductible.

Simply contact one us below and we will take you through the procedure for submitting your donation.

PUMP and our 400 families, and growing, thank you in advance for your generous support.

Portland-Upper Mount Bethel Food Pantry, Inc.
P.O. BOX 69 (mailing address) • 111 State Street (physical address) • Portland, PA 18351

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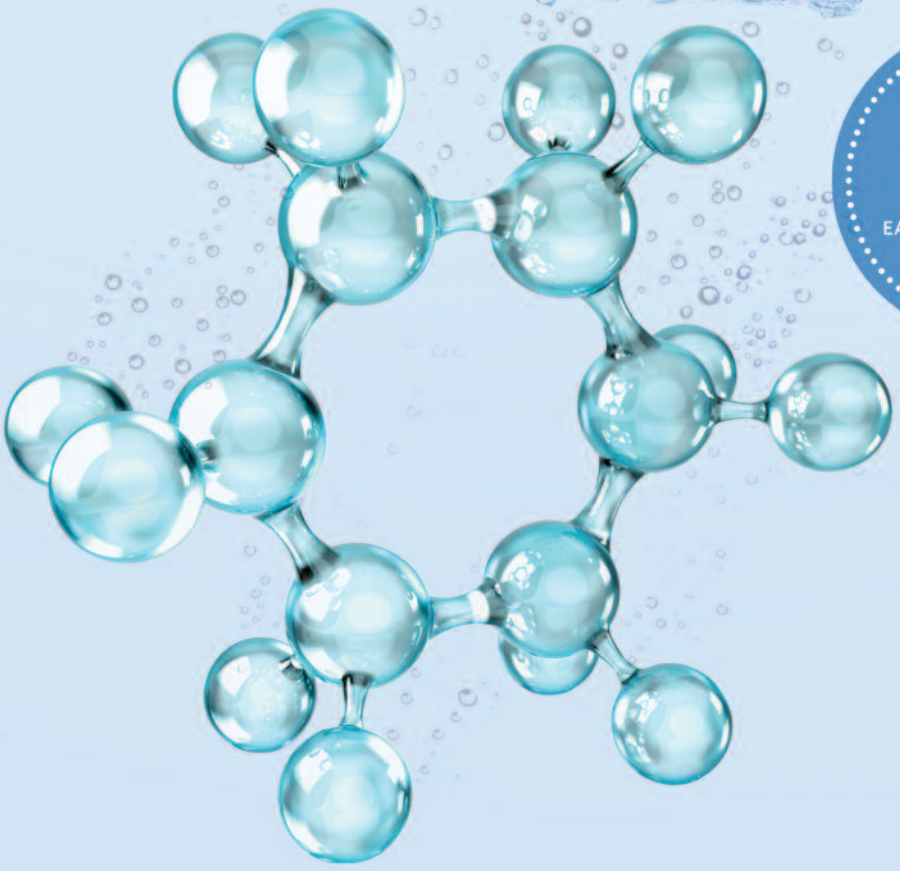

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