Drug Development & Delivery

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Global Markets & Forecasts

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

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Drug-Device Market

"Overall, the combination product industry is growing relatively rapidly, with particular dynamism in successful niche products, and attracting a lot of start-up capital for R&D and developmental companies. Established products, such as drug-eluting stents, anti-microbial catheters, and photodynamic therapy, represent fairly large markets. But going forward, the fastest growth will probably be in even newer areas involving nanotechnology-enabled products."

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Diabetes Diagnostic Testing

"The potential human and economic costs of the diabetes epidemic are staggering, but the opportunity to reverse the health and financial toll by bringing the epidemic under control also offers great rewards. There is a pressing need for better diabetes management solutions to track and diagnose this disease, and avoid the human and economic costs of its complications at an early stage.

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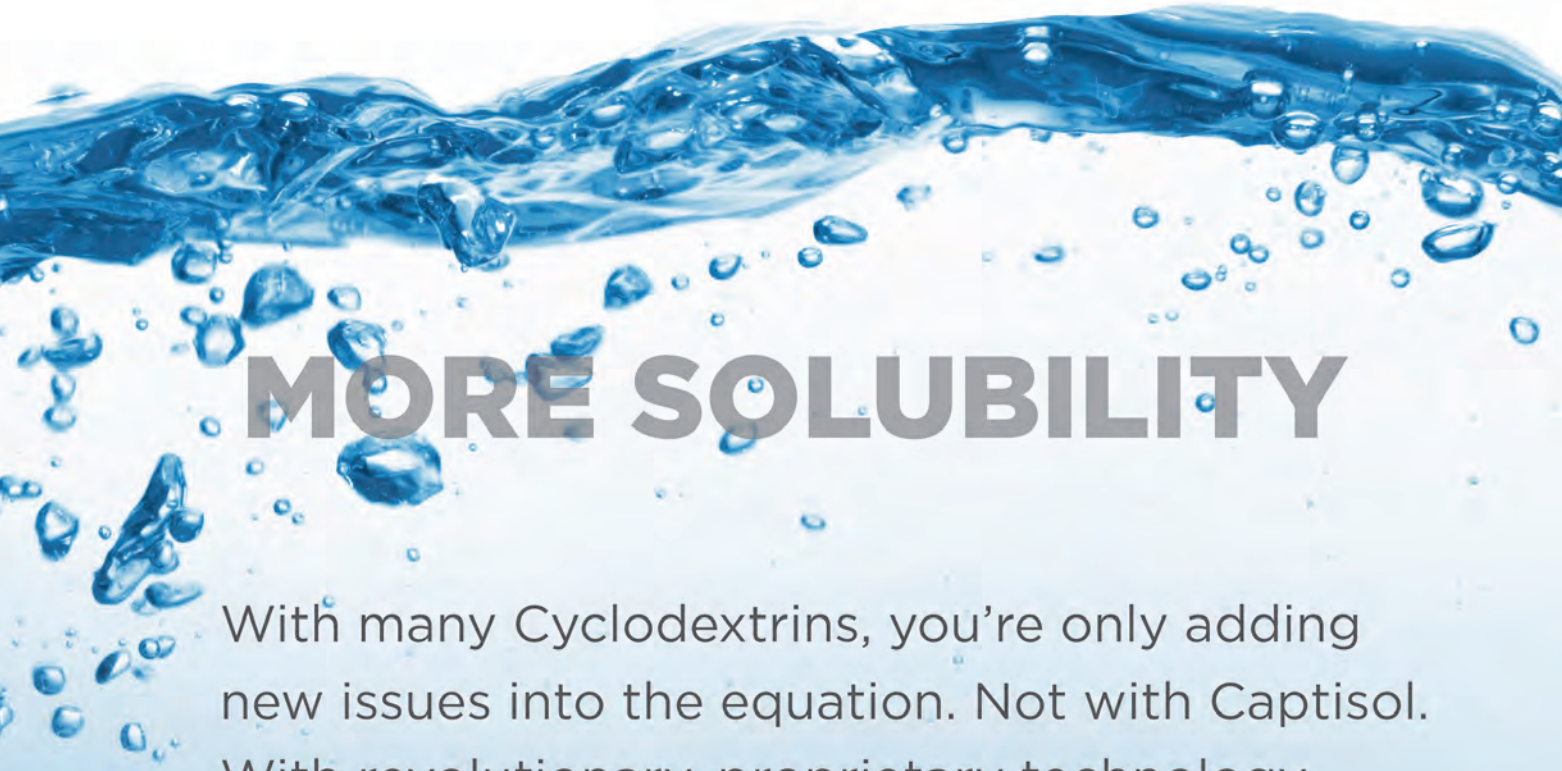

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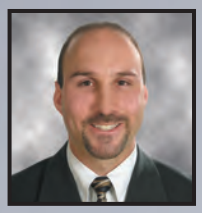

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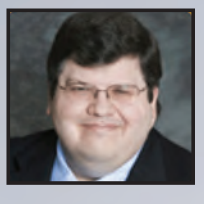

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Protein Reprogramming Method Might Yield Rich Source of Heart Cells for Cardiac Repair

A new study appearing in STEM CELLS Translational Medicine (SCTM) describes a highly efficient, protein-based method for turning fibroblasts — the most common cells in connective tissue — into cardiac progenitor cells (CPCs). The results could lead to a much-needed new source of cells for regenerating the heart. Equally exciting is that the technology also converts the fibroblasts directly to CPCs, skipping an in-between and significantly speeding up the process.

Stem cell transplantation has shown great promise in helping repair a damaged heart, but finding the best source of these cells in quantities large enough for clinical application has been a challenge. Some success in coaxing induced pluipoent stem cells (iPSCs) to become cardiomyocytes (heart muscle cells) has been accomplished using genetics, but safety issues stemming from the integration of foreign genes into the host and from the use of viral vectors are a concern.

Proteins can briefly modulate the gene expression of the host cells, leading to complete transformation of the parental phenotype using a method that is virus-free and does not introduce any foreign genetic material into the recipient's system. While researchers have had some success in using proteins to reprogram cells, the number of cells that turned into the intended cell types remains low.

In the SCTM study, a team of scientists from Guangdong General Hospital, Guangzhou Medical University (GMU) and Wayne State University (WSU) reported they overcame this problem by using a simple, non-viral based protein delivery system consisting of four modified transcription factors (GHMT) and three growth factors. When fibroblasts from human skin were reprogrammed to become CPCs, the yield of CPCs was an amazing 80 percent. When these cells were then transplanted into rat hearts after a heart attack, cardiac function showed improvement.

Xi-Yong Yu, MD, PhD, of GMU's Guangdong Cardiovascular Institute, is co-lead investigator of the study. "The resulting CPCs were similar to cardiac progenitors in appearance, colony formation, activation of cardiac marker genes and cardiac lineage differentiation potential," he said. "We believe this protein reprogramming strategy lays the foundation for future refinements and might provide a source of CPCs for regenerative approaches."

Co-lead investigator Jianjun Wang, PhD, of the Biochemistry and Molecular Biology Department in WSU's Medical School, added that using undifferentiated CPCs as the building blocks to grow specific types of heart tissue is of great interest for regenerating the myocardium. "However," he cautioned, "it will be critical to determine whether key physiological properties are faithfully reproduced after reprogramming. Further study is also needed to investigate the characteristics of in vivo differentiated cardiomyocytes and vasculatures from protein-induced CPCs in their native environment, which might promote survival, maturation and coupling with neighboring cells."

Yigang Wang, MD, PhD, Director of Regenerative Medicine at University of Cincinnati Medical Center, is another noted researcher focused on the technology involved in producing CPCs with high efficiency. He commented on the Yu-Wang team's findings, saying that he "hopes that it will lead to a new source of abundant seed cells for cardiac tissue engineering in a clinical setting."

Oxford Gene Technology Licenses SNP Probe Technology to Baylor Miraca Genetics Laboratories

Oxford Gene Technology (OGT), has entered into a deal with Baylor Miraca Genetics Laboratories (BMGL), licensing the use of OGT's proprietary single nucleotide polymorphism (SNP) array probe technology. This novel technology overcomes the limitations of restriction enzyme-based SNP probe approaches previously employed at BMGL for loss of heterozygosity (LOH) detection, allowing accurate array-based analysis of low-input DNA samples.

Based in Texas (US), BMGL provides the highest quality genomic services across the US and to over 16 countries worldwide, and as part of this objective, utilize aCGH arrays containing both copy number variation (CNV) and SNP probes to identify a broad range of genetic syndromes. For BMGL, OGT's intensity-based SNP probe technology provides a superior alternative to restriction enzyme-based approaches, which are unable to accurately analyze small amounts of DNA. The probes designed by OGT target each SNP allele, with the intensity ratio following hybridization allowing reliable detection of LOH. To ensure robust and high-resolution LOH analysis, each probe set has undergone extensive optimization and validation.

"We are dedicated to the rapid delivery of the most accurate genetic analyses," said Vice President of Operations at BMGL, Mr. Sean Kim. "Through the application of OGT's technology, we are now able to provide reliable array-based analysis of both copy number variation and loss of heterozygosity for challenging samples. We are now also looking to other areas of genetic analysis, expanding the use of this technology toward our complete portfolio."

OGT's SNP probe technology is a key component of its extensive range of aCGH arrays covering multiple application areas, including cancer and constitutional research. The latest product in development utilizing this technology is the CytoSure Constitutional v3 +SNP array, which provides enhanced exon-level coverage of all developmental disorders. As a fully comprehensive approach to its genetic analysis strategy, BMGL also utilizes OGT's Cytocell FISH probes, and following a significant and successful validation program, plans to further extend the use of these probes.

Dr. Mike Evans, CEO of OGT, commented "Through granting the license, we are proud to be advancing the capabilities of such a prominent organization as the BMGL with our SNP array probe technology and Cytocell FISH probes. This presents just the first step in an ongoing relationship, and we look forward to continuing this close cooperation."

First Patient Dosed in Clinical Trial of Halozyme's Investigational Drug in Combination With Merck's Immuno-Oncology Drug

Halozyme Therapeutics, Inc. recently announced the first patient has received its investigational new drug, PEGPH20 in combination with Merck's KEYTRUDA (pembrolizumab) in a clinical trial to determine the maximum tolerated dose of PEGPH20 and antitumor activity of the combined therapies. The Halozyme-sponsored Phase Ib study is being conducted at a number of leading sites in the US, and is evaluating patients with advanced non-small cell lung and gastric cancers.

Following an initial dose-escalation portion to determine the maximum tolerated dose of PEGPH20 in combination with KEYTRUDA, the study will be expanded to determine antitumor activity, including overall response rate, duration of response, and progression-free survival in patients with high levels of hyaluronan (HA). HA is a glycosaminoglycan, or chain of natural sugars in the body that can accumulate around cancer cells creating high pressure in a tumor, constricting blood flow, and thereby reducing access of chemotherapy and immunotherapeutic agents, like KEYTRUDA. PEGPH20 degrades HA, reducing tumor pressure and increasing blood flow to treat the tumor.

During the expansion portion, the study seeks to enroll approximately 50 patients with high HA tumors who have relapsed or refractory stage IIIB/IV non-small cell lung cancer treated with at least one platinum-based regimen, or who have recurrent locally advanced/metastatic gastric adenocarcinoma who are also PDL-1 positive and have failed at least one chemotherapy regimen.

"Our goal is to make a difference in the lives of patients, and that starts by studying the safety, tolerability, and efficacy of PEGPH20 in a broad range of tumor types and in combination with a broad range of therapeutic agents," said Dr. Helen Torley, President and CEO of Halozyme. "With this study, we see an opportunity to expand the potential benefits of immunotherapy through the novel combination of KEYTRUDA and PEGPH20, targeting two of the most difficult to treat cancers."

PEGPH20 (PEGylated recombinant human hyaluronidase) targets the degradation of hyaluronan (HA), a chain of natural sugars that can accumulate around cancer cells, inhibiting other therapies. By degrading HA, PEGPH20 may increase the access of co-administered chemotherapeutic and immunotherapeutic agents. The FDA granted orphan drug designation to PEGPH20 for treatment of pancreatic cancer and fast track for PEGPH20 in combination with gemcitabine and nab-paclitaxel for the treatment of metastatic pancreatic cancer. Additionally, the European Commission, acting on the recommendation from the Committee for Orphan Medicinal Products of the European Medicines Agency, designated investigational drug PEGPH20 an orphan medicinal product for the treatment of pancreatic cancer.

EMD Millipore to Provide Provantage End-to-End Solution for Development & Manufacture of Biosimilars Under Strategic Alliance

EMD Millipore recently announced it has entered into a strategic alliance with Turgut Ilaç and will provide their Provantage End-to-End services for development and manufacturing of biologics.

EMD Millipore's Provantage End-to-End solution is a comprehensive suite of products and services enabling biopharmaceutical companies to accelerate progress of molecules into the clinic and toward commercialization. The turnkey package includes process development, cGMP manufacturing, facility design, equipment for pilot plant production, process and equipment training, technology transfer, equipment qualification and set-up for commercialization.

Under this multi-year agreement with Turgut Ilaç, EMD Millipore will provide process development, equipment for a pilot facility, cGMP manufacturing, facility design, and ultimately, technology transfer of the manufacturing process to Turgut's facility for commerical production. Use of an identical template in both pilot- and commercial-scale facilitates technology transfer.

Phase I of the agreement will focus on monoclonal antibody biosimilars for non-small cell lung carcinoma and rheumatoid arthritis, the first molecules of Turgut's biosimilar pipeline that will be supported by EMD Millipore under this strategic relationship. Financial terms were not disclosed.

"Biosimilars represent an important new therapeutic option and many biopharmaceutical companies around the world are investing in their development and manufacture," said Udit Batra, President and CEO, EMD Millipore. "We are excited to work with Turgut Ilaç, leveraging our end-to-end offering to help create and optimize processes and manufacturing facilities for these molecules."

"Turgut Ilaç was one of the founding companies of the pharmaceutical sector in Turkey and one of the first to develop generics," said Kaya Turgut, Founder and Chairman of the board, Turgut Ilaç. "Our business model has now evolved to focus on development and manufacture of industry leading biosimilars. To support this inititiative, we sought a provider with strong scientific knowledge and expertise that could provide turnkey support encompassing everything from process development to commercial production. With this relationship, we gain access to expertise and capabilities that will not only allow us to establish robust processes, but make the transfer of those processes from pilot scale to commercial facilities much easier and faster."

Planbox & Novatek International Announce Exclusive Agile Innovation Partnership for Life Sciences

Planbox has entered into an exclusive worldwide strategic partnership agreement for Planbox Innovate (formerly BrainBank Innovation Management Software), which will be marketed as NOVA-INNOVATE by Novatek International to the Pharmaceutical and Biotech industries globally.

Both companies have worked very closely to launch a new solution that takes advantage of the 16 years of pioneering experience Planbox has in the Innovation Management and Work Management market, with 400+ deployments. NOVA-INNOVATE's rule engine, templates, and agile workflow have been configured based on Novatek's deep understanding and knowledge of the needs of pharma and biotech business, intellectual property, and regulatory requirements.

"Novatek has built incredible expertise with a close working knowledge of what life sciences organizations need to be successful in a highly demanding, regulated yet fast changing environment," said Ludwig Melik, CEO of Planbox. "We are delighted to have the opportunity to collaborate and leverage their vast experience to better serve our clients."

"Planbox Innovate has a proven track record of creating tremendous value for clients. It has been battle tested since 1999 and has powerful design, configuration, and workflow capabilities to meet the most complex and advanced needs of our clients with zero customization," added Parsa Famili, CEO of Novatek International.

Planbox is the pioneering provider of cloud-based Agile Work Innovation solutions. Its mission is to help organizations thrive by transforming the culture of agile work, continuous innovation, and creativity across the entire organization. Its family of products includes Collaborative Innovation Management and Work Management applications. Planbox is designed to be the agile work innovation tool for everyone, built for companies and teams of all sizes and trusted by some of the world's most recognized brands including Bridgestone, CGI, Nestle, Sempra Energy, Starbucks, Philips, and Verizon with millions of internal and external users.

Novatek International is leading global manufacturer of regulatory compliant LIMS, quality management and other specialized software systems for the Life Science industry. With over 15 years of experience meeting user requirements, Novatek has developed comprehensive business ready, out-of the-box solutions for pharmaceutical, biotech, and other healthcare industries.

DRUG-DEVICE MARKET

Joining Forces: Global Markets for Drug-Device Combinations

By: Kevin James & Kevin Gainer, BCC Research

INTRODUCTION

Products that combine a drug or biologic with a device, such as drug-eluting stents and drug delivery systems, can offer valuable approaches for treating disease. As the purpose of most drug-device combination products is to either augment a device's efficacy and/or safety through the use of a drug coating, or to use a device to deliver a drug locally and in that way increase efficacy of treatment, these combination products are generally used to treat conditions rather than cure them.

However, some do affect a cure, and the possibility of more curative devices brought to market cannot be discounted as the relevant sciences advance. Consequently, the development of the market for combination products is closely related to the drug delivery systems sector, which represents a vast area of research and the demand for sophisticated drug delivery devices behind many novel product developments. Advanced drug delivery devices offer increased efficiency, improved performance, and convenience.

It is anticipated that combination products will enable the use of therapy candidates that cannot currently be used alone due to systemic effects and toxicities. Combination product technology will enable safer and more effective technologies due to careful and precise drug targeting, local administration, and individualized therapy. These technologies have paved the way for combination products that will help patients suffering from cancer, heart disease, multiple sclerosis, cerebral palsy, spinal-cord injuries, anemia, hepatitis, rheumatoid arthritis, diabetes, and other serious diseases and conditions.

The number of product categories and individual product offerings in the drug-device combination market has grown to be relatively large. Although a couple of categories (drug-eluting stents and antimicrobial catheters) together account for the majority of sales, numerous developmental companies are pursuing products that almost undoubtedly will significantly affect efficacy, outcomes, and economics in medical procedures in the years to come.

According to BCC Research, sales of drug-device combination products reached $21.4 billion in 2013 and $22 billion in 2014. This market is expected to grow to $31 billion in 2019, with a compound annual growth rate (CAGR) of 7.1% from 2014 to 2019.

MARKET ANALYSIS

The combination products industry includes makers of drug delivery systems, gene therapy systems, personalized medicine drug-device combinations, biological-device combinations, nanotechnology, and certain other products for diagnostic and therapeutic treatments of cardiovascular, metabolic, oncologic, and other disorders.

Overall, the combination product industry is growing relatively rapidly, with particular dynamism in successful niche products, and attracting a lot of startup capital for R&D and developmental companies. Established products, such as drug-eluting stents, anti-microbial catheters, and photodynamic therapy, represent fairly large markets. But going forward, the

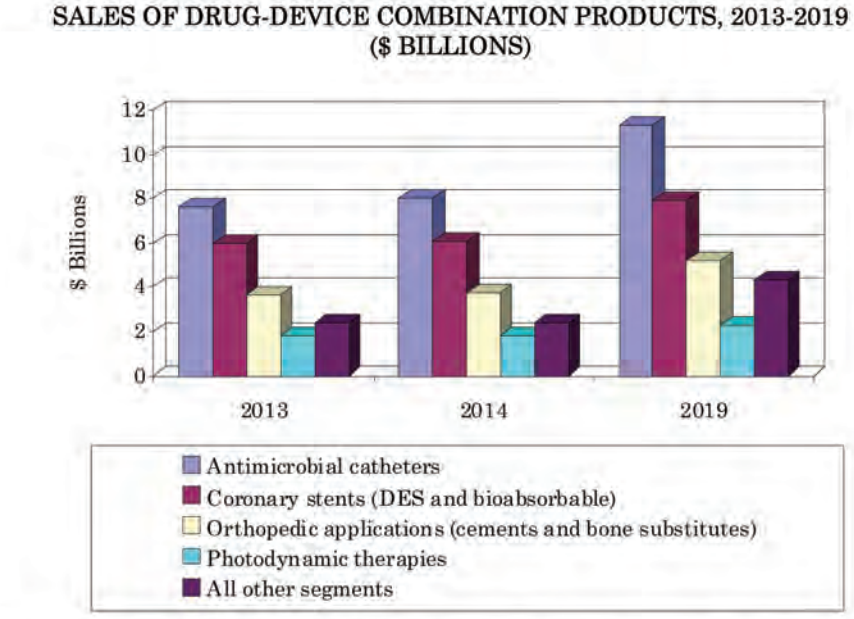
fastest growth will probably be in even newer areas involving nanotechnology-enabled products.

It is anticipated that combination products will enable the use of therapy candidates that cannot currently be used alone due to systemic effects and toxicities. Combination product technology will enable safer and more effective technologies due to careful and precise drug targeting, local administration, and individualized therapy. These and other drivers have paved the way for combination products that will help patients suffering from cancer, heart disease, multiple sclerosis, cerebral palsy, spinal-cord injuries, anemia, hepatitis, rheumatoid arthritis, diabetes, and other serious diseases and conditions.

The R&D effort and accompanying expenditures in combination products is very substantial. A large segment of the market is drug-eluting stents. The DES stent market historically was growing at approximately 8% per year. That growth trend is projected to slow, however, to a CAGR of 5.3% due to commoditization of the stent market and concerns about over-use. Thus, the market for drug-eluting stents is projected to increase from $6 billion in 2013 to $7.9 billion in 2019.

Demand for bone graft substitutes and antibiotic bone cements is growing at a healthy 7% CAGR. Many of the newer niche categories, such as ocular products, drug-eluting beads, and many types of nano-based products, will show significant growth in the range of 8% to 10% per year. Aggregated, these newer niche segments are growing at about 12% per year.

FIGURE 1



Source: BCC Research, "Global Markets for Drug-Device Combinations" (PHM045D), January 2015

TECHNOLOGY & PATENT ACTIVITY

The drug-device combination industry is a prototypical example of technological innovation as reflected in the patent database. In fact, if only two words were allowed to describe the salient characteristic of the overall industry it would be "technological dynamism." Indeed, the number and technological import of patents relating to products in this industry reflect the enormous efforts and expenditures to develop breakthrough therapies for serious human diseases.

Large numbers of patents are being issued, almost on a weekly basis. Technology developments are key forces in the industry. Some examples of this are in the area of nanotechnology-enabled devices and small particles, medical device coatings, and delivery systems. All of this activity is driven by the fact that from the standpoint of drug-device combination developers, there is large clinical potential as well as substantial investment returns.

Throughout the past 5 years, each year, about 300 original premarket applications for combination products have been received at the FDA's Office of Combination Products. According to the latest data, the FDA received 266 original premarket applications for combination products in 2012, 285 applications in 2011, and 311 in 2010.

The FDA obviously is a central focus in this industry. Comparable regulatory entities exist overseas. In fact, as the combination product industry has evolved, the FDA's oversight of this particular segment has become ever more focused.

Because combination products involve components that would normally be regulated under different types of regulatory authorities, and frequently by different FDA Centers, they also raise challenging regulatory, policy, and review management issues. The differences in regulatory pathways for

"Overall, the combination product industry is growing relatively rapidly, with particular dynamism in successful niche products, and attracting a lot of startup capital for R&D and developmental companies. Established products, such as drug-eluting stents, anti-microbial catheters, and photodynamic therapy, represent fairly large markets. But going forward, the fastest growth will probably be in even newer areas involving nanotechnology-enabled products."

each component can impact the regulatory processes of all aspects of the product life cycle, including preclinical testing, clinical investigation, marketing applications, manufacturing and quality control, adverse event reporting, promotion and advertising, and post-approval modifications.

HIGHLY ADVANCED TECHNOLOGIES AS A MARKET CORE

The pharmaceutical industry spends more on R&D, relative to its sales revenue, than almost any other industry in the US. According to various estimates, the industry's real (inflation-adjusted) spending on drug R&D has grown between three-fold and six-fold throughout the past 25 years, and that increase has been closely matched by growth in drug sales.

The range of R&D re-investment as a percentage of sales is anywhere from 2% to 25%, depending on the company. Total world pharmaceutical and healthcare R&D is approximately $100 billion per year.

Despite those increases, there has been little change in the number of innovative new drugs approved for use each year, even though the federal government has streamlined its drug approval process. And, only about one-third of the drugs approved annually in the US are new compounds; the rest represent modified forms of, or new uses for, existing drugs.

However, combination products represent an area of growing potential as more and more incorporate cutting-edge, novel technologies that hold great promise for advancing patient care. Beyond drug-eluting stents and inhaled insulin, breakthrough new products approved after the FDA's OCP was established include drug delivery systems, pharmacogenomic drug-device combinations, nanotechnology, gene therapy systems, and products for many other diagnostic and therapeutic treatments.

Firms develop new drug products in response to various factors. These include likely demand in a given drug market, influenced by available health insurance coverage; doctors' prescribing practices; demographic changes; government policy toward drug safety and innovation; and the pace of scientific advances in the understanding and treatment of disease. A foundation of combination products is that they typically rely on very sophisticated scientific technologies, such as nanotechnology, genomics, molecular diagnostics, tissue engineering, and stem cell research. In addition to these technologies, the mere convergence of regulated articles fosters novel approaches to treatment and diagnosis: the combinations allow the best of all worlds to confront today's health problems.

NANOTECHNOLOGY & COMBINATION PRODUCTS

Nanotechnology applications in drug delivery constitute about half of the applications of nanotechnology in medicine. In vitro and in vivo diagnostics and implant technology are the remaining successful realms. There is a large and growing number of organizations involved in drug-device or combination product applications that involve nanotechnology concepts.

Examples of companies involved include Cerulean Pharma, which has a liposomal nanopharmaceutical, CRLX101, currently in development. Immune Pharmaceuticals (Cambridge, MA) is evaluating the use of its NanomAb platform, a second-generation antibody drug conjugate technology, along with chemotherapeutics.

Celgene markets the nanotech combination drug Abraxane. In May 2014, AADi LLC, a clinical-stage biopharmaceutical company focused on treating diseases uniquely suited for

nanotechnology approaches, licensed ABI-009 from Celgene. ABI-009 is the nanoparticle albumin-bound version of the mTOR inhibitor sirolimus or rapamycin and leverages the same technology behind Abraxane. Abraxane is a protein-bound, injectable formulation of paclitaxel, a mitotic inhibitor drug used in the treatment of breast cancer. In this formulation, paclitaxel is bonded to albumin as a delivery vehicle.

The FDA approved Abraxane in 2005, and the European Medicines Agency approved it in 2008 for breast cancer, in which cancer did not respond to other chemotherapy. A Phase III trial reported in 2010 showed positive results in first-line non-small-cell lung cancer (NSCLC) when compared with Taxol. However, in 2012 at the American Society of Clinical Oncology meeting, researchers reported that Abraxane did not extend life compared to traditional, and much lower cost, treatment regimes. Total revenue from the sales of Abraxane is presently about $350 million per year. Celgene has said it expects revenues to exceed $1 billion annually if Abraxane is used for other types of cancerous tumors.

As of mid-2014, at least 150 nanotech-based drugs and delivery systems and an additional 140 devices or diagnostic tests were in preclinical, clinical, or commercial development. There are at least 50 actually vended drugs or devices that are wholly nanotechnology based according to Nature Biotechnology. The National Science Foundation has predicted that nanotechnology will produce half of the pharmaceutical industry product line by 2015.

World demand for nanomedicines, not all of which are combination product based, is forecast to increase annually by about 12% to 15%, reaching at least $95 billion by 2019. Therapeutic monoclonal antibodies are expected to comprise a significant portion of the nanomedicine market, as more than a third of biotechnology development projects are seeking to apply those proteins to treat a wide array of conditions. That sector alone was estimated to generate $31 billion in 2012. Other major nanomedicine market segments include polymer-based drugs and crystalline nanomedicines. The global nanomedicine market for the central nervous system (CNS) products market is expected to grow to $29.5 billion by 2016. The anticancer products market is expected to reach $12.7 billion by 2016.

At present, there are more than 22,000 scientific publications and 1,500 patent applications per year related to nanotechnology. The exponential increase in scientific publications and patents is the result of increased discovery and investment in nanotechnology that will likely result in substantial and continual changes in products falling under the regulatory authority of the FDA. The FDA has acknowledged that these increases in the discovery, research, and marketing of combination products will have a significant impact. ◆

This article is based on the following market analysis report published by BCC Research: Global Markets for Drug-Device Combinations (PHM045D) by Kevin Gainer.

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

BIOGRAPHIES

Kevin James Kinsella is a New York City-based healthcare and medical communications professional with more than 15 years of experience in the private and public health sectors.

Kevin Gainer holds both BA and MA degrees in Quantitative Economic Analysis and Forecasting, and has 26 years of economic forecasting, industry intelligence, and market research experience.

STEM CELL MARKET

Stem Cell Therapy to Redefine Regenerative Medicine

By: Jane C. Andrews, PhD, Frost & Sullivan

INTRODUCTION

Faced with increasing challenges, such as costly treatments and treatments that are palliative rather than symptomatic, the global healthcare industry today is gradually transforming itself. With few existing therapies capable of curing or significantly changing the course of a disease, healthcare providers are starting to look toward regenerative medicine as a viable alternative.

Regenerative medicine represents a new paradigm in human health with the potential to resolve unmet medical needs by addressing the underlying causes of diseases. It has the potential to cure diseases like we have never seen before. Because of this, the market, especially in the area of stem cell therapy, will continue to experience positive growth, boosted by support from other sectors.

Regenerative Medicine initiatives are now attracting new public and private funding. Although Stem Cell Therapy will continue to be the largest market segment of Regenerative Medicine, cross segment therapies that combine the use of immunology, genetic, and stem cell therapy are rapidly advancing.

Regenerative medicine has also been an area of interest for major pharma companies, many of which have set up their own R&D units or have acquired stakes/invested in regenerative medicine companies. Major pharmaceutical companies that have done so include Pfizer, Johnson & Johnson, and Teva Pharma.

WHY STEM CELL THERAPY?

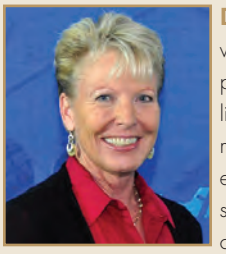
In this space, cell therapy is the fastest growing segment of regenerative medicine and also the largest. Globally, the stem cell therapy market is expected to be worth $40 billion by 2020 and $180 billion by 2030.

Cell therapy involves the use of living cells to replace or augment damaged or diseased cells and tissues. It has been used for various conditions. The largest number of marketed cell therapy products is used for the treatment of notably non-healing wounds/skin (46%) and muscular-skeletal injuries (35%). This trend will change as more and stem cell therapy products for cancer and heart disease complete their clinical trials and are approved for market release.

Factors that are driving stem cell manufacturing in the short-term include aging populations in need of alternative medicine and in the long-term, new evidence that stem cell therapy works. However, an area of concern in the immediate future and long- term remains the lack of early stage funding and the inherent variability in living cells culture and manufacturing.

Despite this, it is expected that investors will increase support for early and mid-stage clinical trials as this fast-moving market continues to develop and show promise. ◆

BIOGRAPHY



Dr. Jane C. Andrews is a Senior Consultant with Frost & Sullivan's Transformational Health practice and considered a thought leader in the life sciences industry. She has a diverse and multidisciplinary background with particular expertise in biomedical and integrated applied sciences, reproductive science, animal health, cell culture and imaging. Her current career focus is in vitro diagnostics, medical devices, alternative animal models, and pharmaceuticals. She earned her PhD in Life Sciences from the University of Wisconsin-Madison. For more information about Frost & Sullivan's global Transformational Health practice, email Kayla.Belcher@frost.com.

COLORECTAL CANCER MARKET

Targeted & Immune System-Based Therapeutics Emerge as Prominent Treatment Modalities

By: Barbara Gilmore, Frost & Sullivan

INTRODUCTION

A vast number and variety of remedies are steadily joining the treatment pipeline for colorectal cancer. High incidence of the disease, unmet clinical needs, and significant commercial potential are attracting drug developers to the market. To stay competitive, participants are focusing on identifying new targets, enhancing overall survival at the early treatment stage, and reducing toxicity.

New analysis from Frost & Sullivan, Product and Pipeline Analysis of the Global Colorectal Cancer Market, finds advanced targeted therapies are dominating the colorectal cancer pipeline, accounting for 60% of the drugs under development. This trend remains in line with the broader oncology market's shift away from standard cytotoxic regimens toward tumor-specific, personalized modalities.

The growing understanding of the molecular make-up of specific colorectal cancer pathways will lead to the evolution of new biomarker targets and additional multitargeted immunotherapies. Biomarker testing, in particular, will become the standard of care, facilitating the selection of a targeted therapy for a patient's individual need (predictive biomarkers) as well as defining the patient's specific tumor type (prognostic biomarkers).

MARKET CHALLENGES

In a crowded market, clear product differentiation and strong marketing efforts will be critical. New solutions must compete with well-established products and therefore, need to demonstrate superior profiles in terms of disease-free survival, time to progression, and overall survival rates. Regulators and payers are intensely scrutinizing novel remedies, and the bar for approval and reimbursement is significantly higher than a decade ago.

Moreover, the emergence of value-based reimbursement in the United States and Western European healthcare has limited targeted therapeutics and diagnostic biomarker tests to patients who will most likely respond to these costly therapies. Payers want to know which treatments are expected to work in order to justify the high costs of targeted regimens.

Producing comparative efficacy data that demonstrates improved survival over competing modalities, along with appropriate pricing strategies, is especially vital because there are multiple tiers of treatment. To that end, head-to-head trials are now commonplace in the colorectal cancer space.

The rising popularity of targeted therapeutics has not affected cytotoxic use, as physicians administer targeted therapies in combination with cytotoxic treatment. In fact, the far-reaching success of immune-based and targeted modalities points to their potential to finally bridge the gap between present cytotoxic regimens and future cancer treatments.◆

BIOGRAPHY

Barbara Gilmore, Senior Industry Analyst for Frost and Sullivan's Transformational Health practice, has consulted for over 26 years with Fortune 500 pharma and biotech companies. She has experience executing commercial diligence for business and competitive intelligence projects, analyzing a broad range of areas, including oncology, cardiovascular, respiratory, and immunology as well as biosimilars, personalized medicine, and formularies in both emerging and established markets. She has extensive expertise in the identification of critical information in strategic decision-making efforts and has an established network of top notch industry contacts. She earned her MS in Comparative Pathology and BS in Human Development, both from the University of California Davis.

SINGLE-USE MARKET

Rise of Single-Use Technologies & Systems in Biopharmaceuticals

By: Kevin James Kinsella & Shalini S. Dewan, BCC Research

INTRODUCTION

Eliminating the risk of contamination is the greatest challenge faced by manufacturers of biopharmaceuticals, and currently, this requires high-level monitoring of critical manufacturing processes. Single-use technology (SUT) aids biopharmaceutical manufacturers in overcoming this challenge by reducing or eliminating the need for sterilization between batches, thereby improving operational efficiency.

Single-use technology first penetrated the market in 1978 in the form of disposable capsules and a range of filters. In 2009, biopharmaceutical manufacturing was revolutionized with the introduction of single-use 2D and 3D process containers and filter assemblies for mixing and storage systems.

Throughout the past decade, disposables and SUTs have become increasingly popular. With SUTs, it is possible to make a small amount of drug products that might be suitable for preclinical and clinical testing. Single-use technology is considered one of the leading areas of development among biomanufacturing companies, as more and more bioprocessing companies are venturing into SUT offerings, not least because SUTs can be applied to the production of all types of biopharmaceuticals.

A shift can be seen in the healthcare industry, from common mega-revenue earner drugs to a multitude of drugs that are useful for smaller volumes of customers. This shift has led to the development of facilities that can produce more than one product, offering flexibility, and scalability. Single-use systems (SUS) address these specialized needs by significantly reducing capital costs and reducing the time-to-market for many drugs.

Companies are eager to develop new SUS, which are used in both upstream and downstream processing of biopharmaceutical production. Indeed SUTs can be implemented at different points along the production process, and this acts as a catalyst for end-user customers to increase adoption of SUTs in their biopharmaceutical production.

The SUT market includes all kinds of systems for upstream processing, such as single-use or disposable bioreactors, membrane adsorbers, media bags, bioprocess containers, disposable mixers, and samplers. Single-use technology is also expanding into downstream processing with many products, such as disposable filter cartridges, depth filters, tangential flow filters, tubing, and connectors.

According to BCC Research (www.bccresearch.com), the global SUT market was valued at just $1.7 billion for 2014. This market is forecast to grow to more than $3 billion by 2019, to register a healthy 5-year compound annual growth rate (CAGR) of 11.7%. The biggest increase will come in the disposable mixing systems segment, which are used in all forms of biopharmaceutical production. This market is forecast to jump to $301.3 million by 2019.

APPLICATIONS

During scale-up of cell culture in the manufacturing of biotherapeutics, specialized approaches are employed to address the unique characteristics of these bioproduction processes. Single-use technologies address these specialized needs of the biotherapeutic development and manufacturing processes.

In the biopharmaceutical industry, the term "single-use," refers to disposable products that are intended for one-time use. Generally, these objects are made from a plastic (polyamide, polycarbonate, polyethylene, polyethersulfone, polypropylene, polytetrafluorethylene, polyvinyl chloride, cellulose acetate, or ethylene vinyl acetate) and are disposed of after use.

Disposables can be rigid (molded systems) or flexible (bags made from multilayer films) and are often supplied pre-sterilized, having been gamma-irradiated at close levels between 25 k and 50 k Gy. This eliminates the need for subsequent sterilization of the equipment, such as the steam sterilization often required with stainless steel equipment. Disposables have numerous advantages, ranging from reducing contaminants to cost reduction.

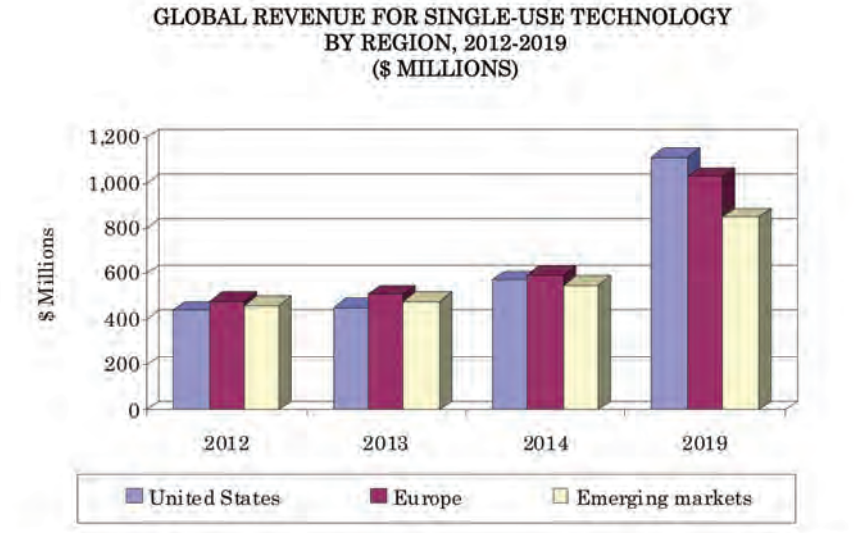
With SUTs, it is possible to manufacture small amounts of drug product that might be suitable for preclinical and clinical testing. Prior to the availability of SUS, the material needed required substantial facilities. These are used throughout the workflow of bioproduction, from buffer and medial preparation to bioreactor cultures for vaccines to the storage and shipping of intermediates and bulk biologics.

Single-use technologies can be applied from upstream bioprocessing through downstream bioprocessing and to formulation and filling. Disposables are used in the same manner as stainless steel counterparts, except that some special consideration has to be given for specific characteristics.

Many biopharmaceutical companies use a variety of SUT products, such as small-scale bioreactors, connectors, and bags. These products offer significant advantages over stainless steel systems, such as flexibility, cost-effectiveness, and decreased time-to-market; hence, SUTs have been widely accepted.

Throughout the past decade, the number and variety of SUS available in biopharmaceutical development and production processes has increased steadily. In 2009, a 35% growth rate was reached, largely from products used for upstream processing. The innovation for other unit operations started in the 1990s with the development and introduction of single-use bags for the storage and transport of buffer and media by the company HyClone, which is now part of Thermo Fisher.

FIGURE 1



Source: BCC Research, "Single-Use Technologies for Biopharmaceuticals: Global Markets" (BIO099B), May 2015

After the shortage of vaccines for the pandemic H1N1 virus in 2009, interest in SUTs surged as vaccine production companies realized that they needed a quick method of avoiding vaccine shortages in the future. The reduction in time required for any drug to reach the market is the key advantage of using SUTs.

SUTS VERSUS TRADITIONAL REUSABLE TECHNOLOGY

Single-use/disposable technology has emerged throughout the past decade as a cost-effective and flexible basis for biopharmaceutical manufacturing. The biopharmaceutical industry is rapidly adopting SUTs for clinical trials, product launches, and commercial production of biomolecules to provide cost-effective and flexible process capabilities. These technologies have requirements, advantages, and disadvantages that differ from traditional reusable technology.

The disposable products that are still

"Throughout the past decade, disposables and SUTs have become increasingly popular. With SUTs, it is possible to make a small amount of drug products that might be suitable for preclinical and clinical testing. Single-use technology is considered one of the leading areas of development among biomanufacturing companies, as more and more bioprocessing companies are venturing into SUT offerings, not least because SUTs can be applied to the production of all types of biopharmaceuticals."

used in bioproduction were introduced more than 30 years ago and include tubing, T-flasks, and pipettes. Single-use technology has become highly complex since then; so much so that they are now also used as alternatives across manufacturing operations.

Disposable devices range from simple equipment, such as transport containers, to entirely closed unit operations. Some SUTs are critical for biopharmaceutical manufacturing (ie, sensors, bioreactors, connectors, distribution assemblies, process fluid mixing and storage systems, material and product storage and cryopreservation systems, and filtration and chromatography systems).

More stringent specifications are required in downstream processing than upstream processing for material robustness and leachables in the implementation of disposable technology. Large-scale purification of scalable tangential flow and depth filtration units now use SUTs.

Novel SUTs for large-scale purification and polishing are now available and widely accepted, including the use of pre-packed, pre-qualified, and pre-sanitized large-scale chromatography columns containing many popular resins. The purification of protein, DNA, viruses, and other high-molecular-weight products, and DNA and endotoxin removal in the polishing steps, are performed with the application of membrane adsorbers. Technologies like simulated moving bed (SMB) chromatography are now becoming popular in the biopharmaceutical industry.

MARKET ANALYSIS

An increase in life-threatening diseases has created a surge in demand for therapeutic drugs. This increased demand has forced biopharmaceutical manufacturers to look for quick and effective ways to manufacture drugs. This in turn has led to the growth of SUTs.

Single-use technologies are widely accepted even by contract manufacturing organizations to increase manufacturing efficiencies. Disposable technologies are widely used in small-scale production and have become important options for some large-scale manufacturing. This will continue to enhance improvements in other areas, such as purification of monoclonal antibodies, recombinant proteins, etc.

Leading players in the SUT market include Sartorius Stedim Biotech, Pall Corp., EMD Millipore, and Thermo Fisher Scientific. According to BCC Research, the worldwide market for all types of single-use products was nearly $1.4 billion in 2013, which increased to $1.7 billion during 2014. The market is projected to be around $3 billion in 2019, growing at a compound annual growth rate (CAGR) of 11.7%.

In terms of overall market share, single-use media bags led with a 13.8% share, followed by bioprocess containers with 12.7% share. Single-use bioreactors had an 11.6% share. Tangential flow filtration systems and the other category of single-use products had 11.2% and 11% shares, respectively.

Tubing and connectors had a 10.2% share of the market, disposable filter cartridges had an 8.3% share, disposable mixing systems had 7.8%, and depth filtration systems had 7.4%. Membrane adsorbers and samplers had 3.9% and 2.2% shares, respectively.

In regional terms, the European SUT market was worth $511.5 million in 2013, and is expected to reach $1 billion in 2019, growing at a CAGR of 11.5%. Companies like Sartorius, Pall, and EMD Millipore have contributed to the growth of the market through their sales of single-use products.

Emerging markets were valued at

$459.7 million in 2012 and are projected to be around $851.7 million in 2019, growing at a CAGR of 9.1%. The major flourishing markets include India, China, and South Korea, as they recognize the benefits of SUTs, such as pre-validation of systems, cost-effectiveness, and fast set-up.

Sales for the US market in 2014 were impressive due to higher sales of Thermo Fisher as a result of its acquisition of Life Technologies in February 2014. With the acquisition, Thermo Fisher gained rights over the vast number of single-use products of Life Technologies. The US market was valued at $573.3 million in 2014. The market is expected to grow at a 5-year 14.2% CAGR to reach $1.1 billion in 2019.

RECENT DEVELOPMENTS

In June 2012, EMD Millipore released data demonstrating successful application of the Mobius Cell Ready 3 L single-use bioreactor for large-scale production of human stem cells on collagen-microcarriers. This application facilitates large-scale production at up to one-third the cost per dose of cells grown in flat culture stacks. Routine expansion of human mesenchymal stem cells (hMSCs) has shown consistent production with cell yields up to 700 million cells in 2.8 L after 14 days of growth.

In May 2013, GE Healthcare acquired Xcellerex. This acquisition expanded GE Healthcare's offerings of SUTs and services for the manufacture of biopharmaceuticals, such as recombinant proteins, antibodies, and vaccines. The acquisition offered strong capabilities in product development and marketing for GE, thus increasing growth in the worldwide market.

In May 2014, Advanced Scientifics (ASI) and Chemic Laboratories declared a 3-year joint cooperation agreement that will enable the two companies to collaborate on a number of product development projects in the pharmaceutical and biopharmaceutical markets, particularly in the areas of leachable and extractable analytical data supporting SUS. Under the cooperation model, the two companies will provide details regarding their SUS. This will allow the users to streamline their processes, and predict material compatibility and regulatory guidance about leachables in SUS.

In August 2014, Progenics Pharmaceuticals, an oncology firm, selected contract manufacturer Gallus BioPharmaceuticals to manufacture the anti-prostate specific membrane antigen (PSMA) monoclonal antibody that is used in Progenics' PSMA ADC (antibody drug candidate) product, which is in ongoing Phase II clinical trials. In its manufacturing facility, Progenics uses a variety of single-use products, such as single-use bioreactors, single-use media bags, etc., in upstream and downstream processing.

Also in August 2014, Patheon Inc. acquired contract manufacturer Gallus BioPharmaceuticals. With the acquisition, Patheon plans to expand its presence in the US outsourcing biological market. Gallus has two mammalian cell culture facilities in the US in Princeton, NJ, and St. Louis, MO, and is one of the major users of SUTs. Its Princeton site is focused on process development and early stage production. Its St Louis site is concerned with commercial manufacturing of biopharmaceuticals and contains both stainless steel and single-use equipment.

Resulting from advantages such as cost-effectiveness, reduction in contamination, higher product efficiency, and reduced time-to-market, the SUT market will be further enhanced in the coming 3 to 4 years.

The driving forces for the SUT market includes a reduced product development timeline, reduction in costs of labor, material and utilities, increased process efficiency, increased productivity, and reduced risk of cross-contamination.◆

This article is based on the following market analysis report published by BCC Research: Single-Use Technologies for Biopharmaceuticals: Global Markets (BIO99B) by Shalini Shahani Dewan.

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

BIOGRAPHIES

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Shalini S. Dewan holds a Master's degree in Pharmaceutical Chemistry with over 14 years of industry experience and was awarded a Gold Medal by the Prime Minister of India for her work.

CELL CULTURE MARKET

3D Cell Cultures: Next Generation & New Challenges

By: Kevin James Kinsella & Robert G. Hunter

INTRODUCTION

3D cell culture has been used by researchers for many years now, with early adoption and now key roles in cancer and stem cell research. Indeed, classical toxicology testing programs have been in place for many decades, and throughout the past 20 years, animal welfare and scientific activities have spurred the development of in vitro testing methods.

Significant growth within the biopharmaceuticals industry is spurring unprecedented innovation in and demand for cell culture products for the purposes of drug discovery and safety testing. While 2D cell cultures have been in laboratory use since the 1950s, the market for 3D cultures, which more accurately model human tissue in vivo without utilizing animal test subjects, has witnessed spectacular growth throughout the past decade.

According to BCC Research, the global 3D cell culture market was valued at just $586 million for 2014. This market is forecast to grow to more than $2.2 billion by 2019, to register a healthy 5-year compound annual growth rate (CAGR) of 30.1%. The biggest increase will come in the area of assay kits, which is forecast to jump to $588 million by 2019. Demand in this area is driven by the fact that assay kits contain all the necessary reagents and specific protocols packaged for laboratory use.

Growth in this industry will be driven by rising R&D spending for many products, such as antibodies and vaccines, soaring biopharmaceutical production, and increasing instances of cancer and liver-related issues. Indeed, these rising rates combined with improved access to consumer healthcare in the US as well as in emerging markets, such as China and India, is expected to spur growth in the 3D cell culture market for the foreseeable future.

NEXT-GENERATIONAL OUTLOOK

3D cell culture has been used for decades, and it has evolved from being messy, laborious, and expensive to much more organized through a broad range of commercial tools. The technology has already enabled groundbreaking knowledge of tissue and cancer behavior.

Positive indicators of future adoption and growth rates, including the beginning signs of delineation of common (not yet best) practices in which specific supplier technologies are mapped to specific applications, offer hope of a coordinated landscape with less market friction than the previous free-for-all applications. This includes 3D continuing to co-exist with 2D in most research application areas. This is partly due to change dynamics, as well as researchers' perception of value in comparing 3D and 2D results for basic insights.

One area in which 3D has the potential to grow into a significantly bigger role than 2D is in liver research, yet substantial progress is required for the development of key standards and best practices in many aspects.

Assuming there are five phases of the growth curve (ie, innovators, early adopters, early majority, late majority, laggards), it appears that skin is the most mature in the early/late majority phase. Liver is in the early adopter phase in four of the top 15 pharma, with the rest still in the innovator phase. Other applications are believed to be in innovator phase and envision roughly 3 years to move from innovators to early adopters. They will depend on the creation of industry and regulatory standards, as well as new internal company drug development processes.

The level of innovation is expected to remain high. Technology requirements will likely approach the sophistication of the organotypic level, which may create tension with requirements in reproducibility, pricing and throughput. In fact, some expect unit price declines across the application landscape, unlike in organotypic skin applications, which have held level prices for many years.

The volume increases to support the substantial growth envisioned will come from an increasing array of applications.

CANCER

Cancer research has long used 3D systems, not only for safety, but also for efficacy testing and basic research. Several areas of unmet need will likely lead in the continued growth of the efficacy role, and they may leverage this experience into other therapeutic areas, particularly in precision medicine applications.

3D cancer co-culture models have been developed in both low-throughput and high-throughput formats, but only cancer cells along with one other cell type (eg, fibroblasts) have been incorporated into models suitable in screening new compounds in a high-throughput manner. In the future, industry leaders see the development of 3D tumor panels for various cancer indications.

Metastases

Metastases cannot be examined in animals or in 2D monolayers in which cells grow only on a flat surface. Researchers have therefore only developed a rough understanding of how they form. Tumor cells alter their surface markers to travel throughout the body. The molecules bind them to a particular area of the body. Cancer cells can then spread freely throughout the body via the circulatory system before taking up residence somewhere else by expressing their original surface markers. Now for the first time, 3D lung tissue is making it possible to analyze metastases.

Tumor Recurrence

The capability of 3D cultures to remain viable for longer terms enables the monitoring of tumor recurrence.

Patient-Derived Cells

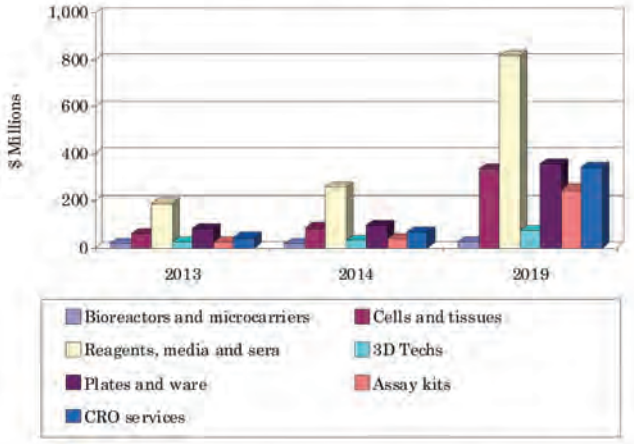
Personalized medicine based on patient-derived cells has been mostly limited to low-throughput preclinical testing to date. Commercial institutes, such as Oncotest and Champions Oncology have developed 3D assays based on indirect patient-derived samples, which have been expanded through the utilization of mouse xenograft models. 3D culture is envisioned to improve this and play a greater role, but developing standards to enable use in drug-screening programs remains a substantial challenge.

LIVER

3D cell culture plays an important role in understanding liver function, as well as dysfunction due to toxins or drug-induced liver injury. The benefit of 3D versus 2D in liver is significant, and adoption is anticipated to ramp sharply in the next 3 to 7 years. This is a

FIGURE 1

THREE-DIMENSIONAL CELL CULTURE MARKET, 2013-2019
($ MILLIONS)



Source: BCC Research, "3D Cell Culture: Technologies and Global Markets" (BIO140A), January 2015

"According to BCC Research, the global 3D cell culture market was valued at just $586 million for 2014. This market is forecast to grow to more than $2.2 billion by 2019, to register a healthy 5-year compound annual growth rate (CAGR) of 30.1%. The biggest increase will come in the area of assay kits, which is forecast to jump to $588 million by 2019. Demand in this area is driven by the fact that assay kits contain all the necessary reagents and specific protocols packaged for laboratory use."

combination of 3D technology delivering on the unmet need left by 2D technology, together with the increasing possibility for regulatory support to coalesce around a specific role for 3D in drug safety testing for liver toxicity and drug induced liver injury (DILI).

This adoption is most likely in sub-segments, such as so-called slow-release (metabolism of compounds) indications. Substantial progress is required in the development of key standards and best practices in many aspects for this role to be defined and made mandatory.

Integration With –Omics

One exciting possibility is that this strong unmet need in the face of the liver's extreme complexity will help drive increased integration of various -omics approaches, along with cell culture and analysis. This will require continued innovation by the 3D community. Lab directors in proteomics have pointed to difficulties with cell extraction from scaffold or gel, as it often ends up being the denatured supernate that is analyzed. Also, many of the biochemical changes currently being investigated occur over very brief time windows, which can easily be missed.

Related technology exists, but it must be further integrated. A single chip can now be used to do thousands of experiments in parallel, thus further leveraging genomic analysis applications. Efforts to translate the chip format to arrays of proteins, however, have largely failed to gain traction in the market. Customers wanting multiplexing capability for proteins have largely adopted the Luminex xMAP technology, which can measure up to 100 different analytes per well. MesoScale Discovery also has some interesting technology in this area. The new paradigm is not only about studying the structure and function of the translated products (ie, proteins) of all the genes encoded in the human genome, but also the million protein-protein interactions, which is known as the interactome.

REGENERATIVE MEDICINE & CELL THERAPY

3D cell culture is expected to play a role in regenerative medicine, initially by helping to test stem cell-derived therapies. This is still largely undefined, but it is envisioned to play out in a manner similar to the testing of biologics during process development. The experiences gained through these biologics research applications will inform and otherwise prepare the 3D field for the therapeutic applications to come later.

3D cell culture has long been used by stem cell researchers, and this trend is expected to continue in research and eventually link to therapeutic applications.

In therapeutic applications, stem cells are derived from either allogenic or autologous models. As an allogenic therapy, one batch of cells is used to treat multiple patients. This approach, which mirrors the traditional pharmaceutical business model, is typically easier to culture, scale up, and automate, and it is likely lower in cost. The disadvantage is the risk of an immune rejection by the patient.

In autologous cell therapy, the inherent inter-donor variability of source material adds a daunting challenge. Thus, the production platform of the future will require significant process flexibility to accommodate unique constraints of individual cell populations, to say the least. Even the best standard operational procedures (SOPs) cannot remove the inherent variability between different batches, and different technicians performing the same actions of a multistep process. Naturally, these factors multiply across environmental parameters (eg, temperature, duration of exposure to enzymes, hydrodynamic forces and fluid shear stress).

There is significant work ahead in

characterizing and testing these processes. The good news is that the requirements for this are in many respects similar to the testing of biologics in development in which 3D is beginning to be applied. This will be an interesting area to watch.

BIOLOGICS DEVELOPMENT

In the development of drugs, the drug product is the focus of characterization and testing. In the development of biologics, the process is essentially the product. From initial clone selection through cell culture and media optimization, scale-up, and manufacturing, the process must be continuously analyzed. Developers must consider the individual adherence characteristics of not only the cell type, but of the particular construction or clone they have selected. They must also consider the properties of a final product, as well as the surface of each culture method employed, including distinctions between methods employed in process development and manufacturing, and between seed expansion and final bioreactor culture.

Thus far, 3D tumor microtissues are being used during biologics development of monoclonal antibodies to study tissue penetration kinetics. Biologics are increasingly being developed for cancer, so this area is envisioned to be a key area to watch.

Researchers are optimistic about the potential for the 3D toolkit of the future to fulfill these requirements, particularly when integrated with -omics.

CHARACTERIZATION OF NEW CELL LINES

There is currently little doubt that long-term passage of cells as monolayers can result in the loss of the ability to respond to external signals. This is demonstrated in 3D by cancer cell lines that when returned to a 3D environment, have an incomplete restoration of the original cancer phenotype. Based on research and interviews, BCC Research hypothesizes that developments in 3D cell culture may continue to illuminate important issues with the widespread use of cell lines that have been established and propagated as monolayers. 3D culture will continue to play a key role in characterizing new and existing cell lines.

CHALLENGES AHEAD

Against the optimism of these exciting possibilities, critical challenges for 3D cell cultures include assay validation, correlation to historical 2D culture results, analytic techniques such as proteomics, and automation. Basic concerns include poor reproducibility between batches of biomimetic scaffolds and the limited ability to scale a single 3D format up or down. Providing fully validated or robust 3D culture solutions is still not possible, as comparable results from different culture systems continue to elude investigators.

Microfluidic systems are proving to be valuable tools, but many researchers continue using conventional cell culture methods. Innovators see this as mainly due to unmet needs in basic technology, compatible detection and readouts, and the lack of fundamental data to bridge the gap between 2D and 3D.

Stem cells hold great promise, but they also bring tremendous challenges, and 3D is a key part of the potential solution set, as substantiated in Chapter 11. In the mid-1980s, cell and germ cell survival and differentiation were worked out using a 3D substratum. Since then, many other types of stem cells (eg, nerve cells, epithelial cells, endothelial cells) have been successfully cultured using 3D systems. Moving forward, 3D culture stands to significantly improve stem cell viability and function, and thus offer a higher degree of efficiency, consistency, and predictability, which is critical for preclinical research, and also key for adoption of stem cells in regenerative medicine.

This article is based on the following market analysis report published by BCC Research: 3D Cell Culture: Technologies and Global Markets (BIO140A) by Robert Hunter.

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BIOGRAPHIES

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DIAGNOSTIC TESTING

Diabetes Diagnostic Testing: A Move From Invasive to Non-Invasive Testing

By: Divyaa Ravishankar, Senior Industry Analyst for Frost & Sullivan's Life Sciences Practice

INTRODUCTION

With each passing year, the scope of the diabetes epidemic becomes more evident. According to the International Diabetes Federation (IDF), there are currently more than 246 million people with diabetes worldwide, and this population expects to grow to 380 million by 2025. It is estimated that at least 50% of individuals with diabetes are unaware of their condition. Diabetes is the fourth-leading cause of death in the US and seventh globally. Its complications include heart attack, stroke, blindness, kidney failure, and amputation.

The potential human and economic costs of the diabetes epidemic are staggering, but the opportunity to reverse the health and financial toll by bringing the epidemic under control also offers great rewards. There is a pressing need for better diabetes management solutions to track and diagnose this disease, and avoid the human and economic costs of its complications at an early stage. Diabetes accounts for approximately 5% to 10% of the nation's health budget.

Figure 1 shows the evolution of the diabetes testing market. Although the third generation is currently dominant, much of the innovation prevails in the fourth-generation testing.

This article will focus on the innovations around self-monitoring glucose meters and continuous glucose monitoring devices. Frost & Sullivan performed in-depth competitive intelligence on some of the technologies and non-invasive techniques to highlight key companies to watch in 2015 and beyond.

INNOVATIONS FOR CONTINUOUS BLOOD GLUCOSE MONITORING (CGM)

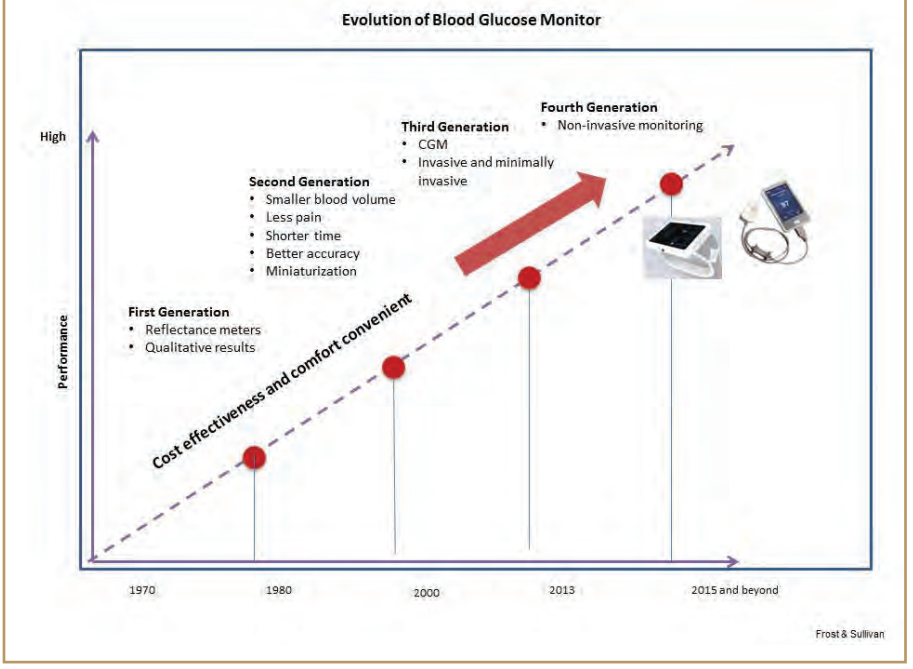
Improvisations have been made at a sensor level to enable the highest possible accuracy. To continuously monitor glucose levels, vendors are proactively researching several methods using different technology traits. Figure 2 gives a comprehensive view of the types of companies pursuing diverse technology channels to effectively differentiate their product.

Many of the products are already in the market, while some are still in the process of clinical trials. The CGM space is also experiencing an uptake of spectroscopic technologies involving Near InfraRed (NIR), Raman spectroscopy, bioimpedance, and thermal emission that will pave the way for non-invasive testing.

ARTIFICIAL PANCREAS (AP), CLOSED-LOOP SYSTEM, BIONIC PANCREAS – IS THIS A POSSIBILITY OR A REALITY?

At the American Diabetes Association, the possibility of an AP becoming a reality was discussed. Several vendors are eyeing AP algorithms that communicate with the pump to initiate a closed-loop system. Major progress has been made in developing this technology and is still considered a near-term technology.

FIGURE 1



A few precursor systems are already in the market. Juvenile Diabetes Research Foundation is massively supporting these studies and has demonstrated the success in low-number patient clinical trials; these are now moving toward commercial development and FDA clearance.

A new company, TypeZero, founded by Dr. Boris Kovatchev and his team at the University of Virginia jointly presented the findings of the Phase II results of the Diabetes Assistant (DiAs) AP algorithm system. The outcomes support the development of larger international clinical trials to confirm the system's safety, efficacy, and commercialization.

ONGOING DEBATE ON HBA1C POINT-OF-CARE TESTS

For years, there have been discussions about the effectiveness of the biomarker HbA1c. HbA1c, which measures glycated hemoglobin, can only be measured every 3 to 6 months. This allows diabetes to progress unchecked for long periods of time and hinders healthcare providers' ability to rapidly evaluate therapy effectiveness. Studies indicate that point-of-care testing or self-monitoring of HbA1c levels should always be verified with laboratory test results, and decisions should not be taken in response to results from CLIA-waived, point-of-care HbA1c meters.

There is an unmet need to control diabetes in a more effective manner. The frequency of available technologies for diabetes monitoring is currently too short (every day) or too long (3 to 6 months). Studies have also demonstrated both glucose testing and the HbA1c testing have low compliance rates for type 2 diabetics. Given challenges of testing, such as the timeframe, frequency, and accuracy, alternative biomarkers have been studied to bridge the gap between the self-monitoring blood glucose (SMBG) and A1C tests to better manage diabetes.

Glycated albumin (GA), a monthly measurement for glycation, is widely endorsed as the best potential marker for assessing diabetes. It is being used with success in a laboratory setting. GA is the ideal analyte to measure short-term glycation; showing protein damage has occurred over the previous two to three weeks.

Epinex Diagnostics has developed the Epinex G1A™ Rapid Diabetes

FIGURE 2

Type	Companies
*Transdermal/ subcutaneous insertion	EyeSense Gmbh (FiberSense), Abbott (FreeStyle Libre)
*Fully implanted sensors (no sensor components seen outside)	Senseonics, Glysens
Eye Implant	EyeSense Gmbh (EyeSense)
Smart Contact Lens	Google/Alcon, Noviosense
*Spectroscopy, heat capacity and electromagnetic techniques (non-invasive)	GlucoTrack, GlucoVista, LighTouch Medical, Echo Therapeutics
Salivary Detection	Quick LLC
Artificial Pancreas	Medtronic, DexCom, Animas Corporation
Software Algorithms	Apple, Samsung, Dreamed

*Transdermal/subcutaneous insertion – These technologies often have the sensor component sticking on the surface or through the skin components, or skin-adhered components
*Fully implanted sensors – These are long-lasting sensors that are surgically implanted by the physician at the insertion site using a sensor delivery system
*Spectroscopic technologies includes NIR, Raman spectroscopy, bioimpedance, thermal emission

Frost & Sullivan

FIGURE 3

Monitoring Index Test. The test is currently under clinical evaluation. Several other companies are pursuing alternative biomarkers to prove efficiency and cater to the unmet need that exists within the diabetic community.

THE SELF-MONITORING BLOOD GLUCOSE (SMBG) MARKET

In the US alone, the SMBG meter contributed $407.6 million in 2014 via the sale of 18.5 million meters. The strip market contributed $3.63 billion with 8.44 billion sold. The SMBG meter market is expected to remain moderately favorable due to the new smartphone connectivity features. However, continuous monitoring and non-invasive methods of glucose testing will still prove to be a threat to the market. With the expensive nature of these tests and technologies, access will still be limited to high-end meters. Most meters today are offered for almost the same price, and every meter is provided with a minimal USB download option; this will provide some market growth.

With the Affordable Care Act, more patients will have secured access to health insurance. This will provide an opportunity for manufacturers to test the undiagnosed population, which accounts for at least 30% of the diabetic community in the US. There is minimal price difference in the cost per strip among manufacturers. The price per strip tends to fluctuate between 35 cents and 45 cents. Due to heavy competition, vendors are focused on volume sales with lower pricing strategies. In most cases, a strong brand value helps in sales, and Tier II vendors tend to suffer the consequences of the negative outcome. The strip market is characterized by heavy price erosion and tends to flatten the growth of the market. The conventional SMBG meter and test strip market is experiencing heavy price pressure, with over 88 branded meters in the US market alone. Given there are heavy reimbursement constraints for mail order pharmacies, the SMBG market reached market saturation in 2013.

In addition, digital health technology is now invading this space. Smart phone connectivity and other features, such as cloud and mobile applications, are luring customers to move to innovative meter technologies. Online sales of meters and strips are increasing. Popular eCommerce vendors (eg, Amazon) are the leaders in online supplies.

Frost & Sullivan outlines interesting companies that have used effective product differentiation strategies to compete in the saturated market. These companies are strong competition for the market leaders, such as LifeScan (J&J), Roche, Bayer, and Abbott. ◆

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BIOGRAPHY

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ALBUMIN MARKET

Global Human Albumin Market: Extra Revenues to Come through Non-Therapeutic Applications

By: Aish Vivekanandan, Frost & Sullivan

Human albumin is widely considered as a plasma replacement or expander for therapeutic purposes. However, for over a decade, the healthcare industry has been exploring the use of human albumin as a non-therapeutic substance/excipient for commercial settings. Across these application areas, emerging opportunities for human albumin as a drug formulation agent, vaccine ingredient, sealant in surgeries, and coating for medical devices and equipment are expected to drive production.

New analysis from Frost & Sullivan, Analysis of the Global Human Albumin Market and Product Pipeline, finds the non-therapeutic use of human albumin as an excipient has generated plenty of interest from the industry and will create a potential customer base comprising academics, research institutes, and pharmaceutical and biopharmaceutical companies. Despite this, very few manufacturers, which include large, medium, and small enterprises, currently supply human albumin for non-therapeutic applications as an excipient.

THE MARKET

Highly consolidated, the market is dominated by a few top participants. There are about 10 key human albumin products from blood plasma manufacturers that meet the therapeutic use of human albumin in fluid replacement therapy. However, the share of albumin in the blood plasma market has decreased from almost 40% in the 1980s to 10% in 2015. As human albumin volume growth is expected to slow down during the forecast period, manufacturers will adopt premium pricing in the non-therapeutic application segment to meet their profit margins.

When it comes to albumin for replacement therapy, a premium pricing strategy could go in vain. This is because pricing pressures, along with limited return on investment and competition from substitute products, pose a challenge to the use of human albumin in replacement therapy.

On the other hand, global increase in the fractionation of blood and rise in demand for human albumin in Asia-Pacific countries, especially India and China, will sustain production rates. In India, regulatory pressures and pricing control of albumin are being eased to meet the therapeutic needs of the population. With shortages in albumin products in the country, global manufacturers are likely to foray into the market, while China's albumin market grows steadily.

The evolving need of albumin use as an excipient will also widen existing market opportunities for blood plasma product manufacturers. Going forward, a large number of biotech and biopharmaceutical firms are expected to develop recombinant versions of albumin to explore its potential in extending the half-life and stability to biologics and biosimilars. There are at least 15 products under clinical trial that involve the use of human albumin as an excipient (stabilizer, drug formulation).

Some of the key products in which albumin is being used as a drug formulation agent, stabilizer, or fusion protein for half-life extension are ABI-009 and rIX-FP. rIX-FP and Albutein for Alzheimer's disease are expected to be launched in late 2015 and 2020, respectively.

Developed by CSL Behring, rIX-FP is a recombinant fusion protein linking coagulation factor IX with albumin. It is indicated for the treatment of hemophilia B, with dosing intervals of up to 14 days. ABI-009 is a nanoparticle albumin-bound version of the mTOR inhibitor sirolimus or rapamycin developed by Celgene, which licensed it out to AADi LLC, a clinical-stage biopharmaceutical company. ◆

BIOGRAPHY

Aish Vivekanandan is an Industry Analyst with Frost & Sullivan's global Transformational Health practice. She has extensive industry knowledge identifying emerging technologies and tracking technological and market developments across the life sciences domain. She has particular expertise in drug discovery technologies and tools, and clinical and in vitro diagnostics. She earned her BS (Hons.) in Neuroscience from University of Michigan. For more information about Frost & Sullivan's Transformational Health practice, email Kayla Belcher, Corporate Communications, at Kayla.Belcher@frost.com.

Drug Development
EXECUTIVE

Eric Goupil
Chief Executive Officer
Unither Pharmaceuticals

Unither Pharmaceuticals: Premeasured Dosage Forms to Improve Medication Adherence

As medicines continually evolve, so does the technology used to deliver them to the patient. Unither Pharmaceuticals is a world-leading provider of sterile blow-fill-seal, and liquid stick-pack dosage forms. Each provides several advantages over traditional delivery systems at about the same cost per dose. The company's vision is to make affordable and user-friendly products that everyone in the world can use to improve their lives. These products are created as a result of its singular focus on convenient, modern dosage forms that are preferred by patients to whom they are offered. Whether a customer works with Unither from an early stage to develop a custom product, brings their own product to them for fill-finish, or brands and markets one of its many ready-to-go formulations, the following single unit doses offer numerous advantages over legacy delivery forms: blow-fill-seal (BFS) technology for sterile unit-doses, liquid or powder stick-pack technology, improved dry formulations, and patented drug delivery systems for per-buccal mucous administration. CEO Eric Goupil recently spoke frankly with *Drug Development & Delivery* about medication adherence, Unither's technology, and some of the challenges that they face.

Q: Can you provide our readers more information about the company, its history, and what makes it unique?

A: A brilliant and fearless friend of mine founded the company in 1993. He purchased a small production plant in Amiens, France, with 17 people and just $2.7 million in annual revenue. He had a singular idea to focus on BFS, and to price the first vial to come off the line the same as the ten-millionth. This was a completely novel and unique proposition, and it was genius because it completely avoids the "chicken and egg" discussion between marketing and manufacturing. The marketing guy will say, "tell me the cost, and I will build the quantity" and the manufacturing guy says, "tell me the quantity, and I will give you the cost." Unither's bet was that charging a small price for first vial would lower the barrier to getting customers in the door, business would develop briskly, and the machines would begin to run profitably. It worked! Initial growth was approximately 30% annually for the first 7 years, and right now, we are at a healthy 15% between organic growth and acquisitions.

We are a contract manufacturing organization (CMO) focused on a few premeasured dosage forms that are preferred by patients. In the US, these are currently sterile blow-fill-seal (BFS), and Unistick® liquid stick-packs. We help our customers develop products that we manufacture and fill, and we also create pharmaceutical products that our customers can immediately brand, market, and sell. There are great market opportunities for our customers worldwide.

We are fully aligned with our customers; when they grow their business, we grow our business, so we work very hard to help ensure their success. We believe that that we are unique among CMOs because we are focused on improving the patient experience, and this makes sense to us because if the patient is happy, the product is successful, the customer is happy, and we are happy.

Blow-Fill-Seal (BFS)

Q: What are some advantages of sterile BFS and liquid stick-pack?

A: Both stick-packs and BFS vials are more convenient, safer, easier to handle, and more portable than bottles. In the US, most liquid products contain preservatives, but there is an increasing realization that many patients are sensitive to these preservatives, particularly in something designed for use in the eye. As a result, we are beginning to see a move toward "preservative-free" formulations, and BFS is an ideal way to achieve this. We help our customers provide a superior product that patients prefer, at no additional cost.

Q: Do you see that "preservative-free" shift and preference coming to the US?

A: We are convinced that our business model and the early adopters of single-unit dose products will be successful in the US. Awareness is definitely growing. We are already seeing a preservative-free preference evolving in the food industry, and this is exactly how the market evolved in Europe: first in food and beverage, and then in cosmetics and pharma. Several preservatives are now banned for use in cosmetics in Europe.

When key opinion leaders are made aware of the advantages of preservative-free formulations, others will follow. The sales data in Europe clearly shows that patients prefer these delivery forms, and we have ready-to-use products that our customers can bring to market right away.

Big advantages are convenience, ease-of-use, and portability, and these significantly help patients to take their medication at the right time, in the right amount (medication adherence).

Adherence is an enormous problem: in the US, up to 50% of prescribed medications are taken incorrectly, contributing to 125,000 early deaths, and costing the healthcare system over $200 billion annually. Our products can help to mitigate some of these issues, and that makes me feel very good.

"Adherence is an enormous problem: in the US, up to 50% of prescribed medications are taken incorrectly, contributing to 125,000 early deaths, and costing the healthcare system over $200 billion annually. Our products can help to mitigate some of these issues, and that makes me feel very good."

Q: Single-unit dosage forms have a longer history in Europe, how are they received there?

A: Extremely well, let me share a couple of example launches in Europe. A popular and established eyewash was formulated with preservatives and sold only in bottles. In 1999, a preservative-free BFS single-unit dose form was brought to market as a box of twenty 5-ml vials (the same amount of product as in the bottle) at the exact same price. The single-unit dose now has four times the sales volume of the bottle; both sales and market share have increased, as well as the market itself.

We have seen the same thing happen with a heartburn medication that after introducing a liquid stick-pack captured 80% of the market in France.

Our products not only increase the market share of the customer's product versus competitors, they actually increase the total amount of product sold, so there is no cannibalization of existing sales.

Q: How do you typically work with your clients?

A: Ideally, we are involved at the start of a project and are approached with a problem rather than a solution. We love to help customers create new markets and new opportunities. We make products for the customers of our customers - the patients. Whenever a new project comes in the door, we look at it through a very patient-centric lens and ask ourselves if it is useful and is it something a patient would pay for. If the answer is no, then we will have a frank discussion about why we believe not, and how the product and patient experience could be improved. We always listen to our customers, but we are invested in their success, and we don't want to simply take their money for a product that we don't believe will succeed.

We are often making products that haven't been seen in the marketplace before, so forecasting sales can be a challenge. A customer may predict sales of 1 million units, and they may end up at 50 thousand or 10 million. Because of this, we approach volume guarantees very differently from other CMOs. Others require customers to commit to specific minimums; we do not. We eliminate the stress of forecasting. Again, we are fully aligned with our customers. We worry about our capacity so they can focus on sales and marketing. Our profitability comes from volume, so if we can help make our customers successful, the volume will be there and everyone benefits.

Q: What are some of the challenges your company is facing?

A: Our products are novel and different, so we need to find innovators willing to become first-adopters. But innovation carries perceived risk. We believe the risk is minimal because there is strong evidence in the marketplace that when customers are offered unit dose at an affordable price, they invariably prefer it. In our experience, there is a tremendous pay-off for innovators. The first-adopter generally captures about 60% of the market, and the total market

Unistick® Liquid Stick-Pack

size grows.

Our job is to make affordable and user-friendly products for everybody in the world, but we have to be price competitive. Because the products are superior to standard forms, many assume they are more expensive to produce. This was perhaps true in the past, but through advanced manufacturing, we have passed the tipping point.

I like to use the analogy of the flat screen television. When they were introduced, everyone immediately realized they were vastly superior to standard CRT TVs, but adoption was slow because of the high cost. As more and more were sold, economies of scale kicked in, and when the cost came down enough, they began to dominate, and now, of course, the market for CRTs is inconsequential.

Q: What's your leadership style?

A: I very much favor autonomy in each division. It's not independence, because there is great collaboration and alignment throughout the organization, but everyone is accountable. The natural tendency in a large company is to centralize decision-making, but to best serve customers and patients, decisions must be made at the local level. This becomes a tremendous benefit because site managers know their customers better than anyone, and they are empowered to make decisions that benefit them. It also allows us to be very nimble - we are now a large global company, but we can move as quickly as a small startup. Decisions that would entail weeks of presentations in a traditional, centralized organization can be made in an afternoon.

Q: What are Unither's growth plans for the future?

A: We are committed to bringing superior products to everyone in the world, so having a global footprint is important. We need to be local at the continent level, and in addition to Europe and the Americas, we already have clients in Asia and Australia.

Growth will continue both organically and by acquisition. As I mentioned, we have grown 15% annually since 2000, and we expect that trend to continue. Organic growth is extremely important. We see some CMOs growing primarily through acquisitions, but robust organic growth means that the organization and business are healthy. We have eight world-class locations on three continents, including our recently acquired plant in Rochester, NY.

Q: How is the Rochester acquisition progressing?

A: We are very much on track. We have invested $15.7 million in phase one to install stick-pack and BFS. Stick-pack is ready to go, and we are already running cGMP batches. BFS construction is progressing well and will be ready in 2016.

I am extremely happy with our US team; they have the customer-focused mindset needed in a successful CMO. Sometimes in Big Pharma the focus is too much on the parent company. When we hire, we ask ourselves "is this the best person to satisfy the customers' needs?" We are fortunate to very frequently answer "yes" to that question. ◆

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MICRONEEDLE TECHNOLOGY

The New Potential of Microneedles for Biologics & Small Molecules

By: Lisa A. Dick, PhD

ABSTRACT

Traditional transdermal patches have been limited to use with a small range of molecules, which is unfortunate, given their patient-friendly features and ease of use. As the pharmaceutical industry continues to expand its offerings to include larger molecules and biologics, new transdermal platforms are also evolving. This article describes how microneedle technology is being applied in two new transdermal systems using solid and hollow microneedles. The solid and hollow microneedle transdermal systems, currently available for clinical trials, have the ability to deliver small molecules as well as biologics, opening up the potential for self-administration of a broad array of Active Pharmaceutical Ingredients (APIs).

INTRODUCTION

Expiring patents, the expanding biopharmaceutical market, and a growing focus on patient preference are all driving changes in drug delivery. For patients with chronic conditions, these changes are likely welcome, as non-compliance among this group has been estimated at 10%.[1-3]

A delivery system that makes it easier for patients to self-administer medications and avoid traveling to a clinical setting for an injection or IV administration holds the potential to improve compliance and convenience. The transdermal patch provides a good example of such a delivery system. Delivery via traditional transdermal patch has been a well-liked option among both patients and providers for many years.[4] Patches beat pulmonary, injection, and intranasal delivery methods in terms of comfort and convenience.

However, traditional patches are only suitable for smaller lipophilic molecules, which account for a very small portion of APIs. Research has continued on transdermal delivery to broaden its capabilities, as this method of delivery has unique advantages, including its rapid onset of action and ability to contribute to higher uptake efficiency.

Now, recent advances in transdermal technologies are making it possible to expand this patient-preferred delivery method to encompass both small and large molecules, including biologics. With these technologies, pharmaceutical companies gain new delivery methods for dermal skin targets or systemic distribution for drugs that enter the lymphatic system.

These advances utilize microneedles — polymeric microstructures — to conquer the limitations of the traditional transdermal patch. There are currently two types of microneedle devices under development.

SOLID MICRONEEDLES

This technology uses a coating of relatively potent molecules and peptides (up to 300 micrograms) that are dried on the tips of a microneedle array. When the patient applies the microneedle array patch with the 3M™ Solid Microstructured Transdermal Systems (sMTS), the solid microneedles (of a set length between 250 micrometers to 700 micrometers tall) penetrate the stratum corneum and remain in

the skin for a wear time ranging from 30 seconds to 10 minutes. During the wear time, the drug releases from the microneedles into the skin. This method of delivery holds great promise for vaccines because it is able to enhance their efficacy by targeting antigen-presenting cells within the skin. With the vaccine kept dry, the patch can be stored at room temperature. Solid microneedles can also potentially improve pharmacokinetics versus a subcutaneous injection for a variety of drugs, assuming the dried drug formulation is stable over time. The 3M sMTS system has been successfully used in Phase I and Phase II clinical trials.

HOLLOW MICRONEEDLES

As opposed to solid microneedles, which use dried API, hollow microneedles allow delivery of liquid formulations of up to 2 mL. This technology is compatible with small molecules as well as biologics, such as proteins and peptides. Hollow microneedles reach into the dermal layer of the skin, a highly vascularized area that makes it ideal for delivery of many treatments.

The 3M™ Hollow Microstructured Transdermal System (hMTS) device is currently in clinical trials. The microneedles are located on a 1-cm^2 polymeric disk, with the specific arrangement of the microneedles adjustable based on drug formulation and targeted delivery site. The microneedle array is attached to a conventional glass cartridge via a sterile flow path. A mechanical spring powers delivery of the formulation from the cartridge through the microneedles. When applied, the microneedles penetrate through the stratum corneum and epidermis to reach into the dermis.

The device is capable of delivering volumes ranging from 0.5 mL to 2 mL, and is compatible with both viscous and non-viscous formulations, with viscous formulations potentially requiring a longer wear time. In hollow microneedle devices, formulations must be chemically compatible with the device, especially upon stability storage and during delivery. Additional physical compability considerations include whether drug molecules are able to withstand shear forces as they flow through the microneedles.

Developers are well aware that design of any new drug delivery device requires close adherence to regulatory requirements for patient-centric design and self-administration. Usability trials conducted on the hMTS have identified design improvements to make it more convenient for patients (especially patients with dexterity challenges) to self-administer. The device is designed in an easy-to-handle size and has a textured grip. Actuation is both visible and audible, as a click sounds when the device is activated. A status indicator window also helps patients see progress of the medication delivery. Features like these help improve patient confidence with self-administration.

SUMMARY

The treatment potential held by biologics and small molecules continues to drive innovations in the pharmaceutical industry. Microneedles provide a promising delivery method for these APIs, and the availability of both sMTS and hMTS for clinical trials moves the industry one step closer to offering a patient-friendly alternative to injections and IV administration. ◆

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BIOGRAPHY

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LOC-BASED DEVICES

Lab on Chip – How Far Are We Along the Road?

By: Divyaa Ravishankar, MS

INTRODUCTION

Lab on Chip (LOC)-based devices are an integration of multiple disciplines and the miniaturization of the major laboratory procedures. Recently, these devices are branching into additional aspects of healthcare, such as drug delivery, stem cell, environmental monitoring, and synthetic biology, owing to the high level of integration required to develop an LOC device.

LOC technology is continually being explored by multiple small-to-medium size companies, predominantly in North America, Europe, and Asia. The technology itself is established as evidenced by organizations having demonstrated working prototypes. Improvements in the manufacturing and microfluidics of the devices, as well as multiplexing complex laboratory processes are where the maximum R&D is taking place. Adoption levels of LOCs have been relatively low across its applications areas. Poor consistency and reproducibility of results using the LOC is hindering adoption. Leading players are trying to resolve this challenge. LOC is still in the early stages of adoption across most application areas. Amongst all application areas, Point-of-Care (POC) and clinical research have the highest adoption rates.

It is important to understand the intricacies involved that cause a potential delay to all the developments and efforts across different applications.

Interoperability with existing laboratory equipment is a major stumbling block for microfluidics.

Existing laboratory equipment will operate at a much larger scale than the microfluidics instruments; comparing results from these two different platforms will prove a major challenge. Incorporating microfluidic devices into existing workflows is a major stumbling block to the adoption of microfluidics into regularized drug screening and discovery workflows. Considering drug screening and discovery is a decade-long process, it is likely to pose significant challenges on scientists to incorporate LOC devices into ongoing programs.

HOSTILE IP ENVIRONMENT HINDERS GROWTH

LOC companies in the diagnostic segment are expected to be hurt the most by this, due to the additional product development associated with regulatory requirements. A related question that remains unresolved is the management of genetic and other medical records. Highly dense biochips, whether microfluidics or microarrays, can produce huge volumes of data about a person very rapidly, not only about gene sequences but also networks and expression levels (which are seen as more important at present due to the low number of genes). The research segments, which rely increasingly on clinical data, for example, morbidity and SNPs, will also be affected. Content is increasingly important and is likely to be limited depending on how these matters play out. Genetic content of targeted analyses tools, such as various DNA and protein arrays, will undoubtedly be influenced by the intellectual property issues.

AUTOMATION OF ESTABLISHED TECHNOLOGIES RESTRAINS GROWTH

The microfluidics market's main competitors are the automation and instrument manufacturers, more so than the companies in the microfluidics market. The reasoning is providers of conventional drug discovery and diagnostic technologies are infusing greater levels of automation and miniaturization into their products. Within the LOC industry itself, the participants have been cautious enough to steer clear of the applications developed by others in the industry. In addition to the automated instruments that vendors of conventional technologies currently offer, they are also proposing high-density microplates, namely 384 and 1536.

MICROPLATES EFFECTIVELY ADDRESS MAJOR CONCERN

Figure1 shows the application of LOCs across different sectors through 2020. Let's take a look at the present status of LOC application:

Point-of-Care Diagnostics - Progress is being made for hand-held portable and benchtop devices, disease detection for infectious diseases, and cardiovascular conditions. This is considered one of the highly competitive markets. Some of the companies to watch in this area include Ubiquitome, InSilixa, QuantuMDx, and Oxford Nanopore.

Drug Delivery - Progress is being made in miniaturizing drug delivery to improve patient adherence and reduce side effects. Slow and controlled drug delivery on a long-term basis is also an area being explored. Companies to watch in this area include Draper Laboratory and MicroChips.

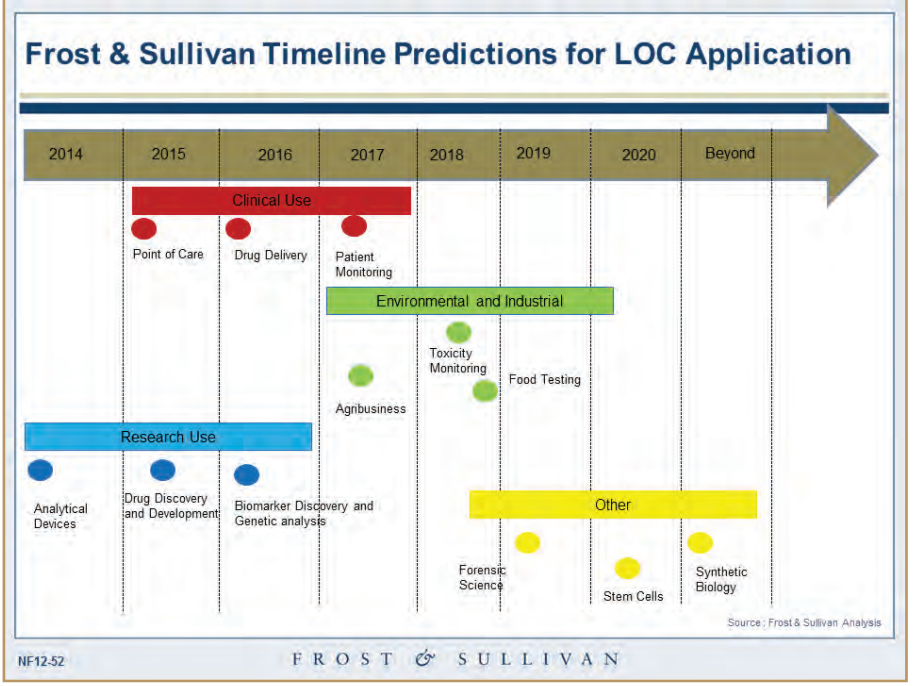
Patient Monitoring - Monitoring chemotherapeutic substances in cancer patients, specifically targeting high-risk and extremely ill patients. Research is underway to enable monitoring of astronauts in space stations for indicators like oxygen and carbon dioxide levels, bone mass, rate of heart beat, and blood pressure. One of the key institutions to watch out for in this area is École Polytechnique Fédérale de Lausanne (EPFL).

Drug Discovery & Development - LOCs are widely used in development of new drugs and improvement of therapeutic effects of present drugs. Examples include the screening of drugs during the manufacturing process and understanding of clinical response of patients to drugs.

Analytical Devices - LOCs have been in this area for quite some time. Miniaturized lab processes, such as PCR, electrophoresis, HPLC, GC, and LC, have already been in the market for a while. A few companies include Perkin Elmer, Agilent Technologies, and Sphere Fluidic.

Biomarker Discovery & Genetic Analysis - LOCs aid in the discovery process of protein biomarkers and has implications in detection and monitoring of disease. Genetic analysis of proteins, enzymes, nucleic acids, and various other molecules can be conducted using LOC devices. They can boost research speed and aid in filling knowledge gaps in disease heterogeneity and molecular pathway analysis. Panasonic (in association with IMEC) and IARPA (Intelligence Advanced Research Projects Activity) are pursuing POC devices for detecting SNPs (Single Nucleotide Polymerisms) and other applications.

FIGURE 1



"The investment ecosystem has significantly changed in recent years due to a rapidly growing interest in organizations toward miniaturizing and developing remote diagnostic capabilities. Speculating a high return, investment bodies are highly interested in LOC and microfluidic chip-based technology, as the constant push in the direction of personalized medicine and better healthcare facilities results in a vital need for cost-effective solutions."

Toxic Monitoring - LOCs use in environmental monitoring comes from their capability to detect pollutants. Algae detection is an area in which LOCs have already been applied. The technology also aids in efforts to prevent contamination of water bodies, essentially protecting food source.

Agribusiness - Remote testing is an important need in the agricultural industry. LOCs have been a platform for the development of food and agricultural testing devices. LOCs also aid in the effort of testing for excessive pesticide usage in farms, improving quality control for wheat, rice, and other agricultural products. A company developing this technology is Acron Genomics.

Food Testing - Microfluidics chips are being developed in multiple companies to aid in discovering food contamination. Meat processing plants, food storage warehouses, and large grocery stores will benefit largely from the development of this testing equipment. Pathogenetix is a company that has already launched its equipment.

Stem Cells & Synthetic Biology - A few developments have taken place in the area of human-on-a-chip platforms; integration of 3D cell cultures to create cell testing platforms on a chip. Eliminating model organisms and human testing, LOCs are finally being employed for synthetic biology-based research.

Biodefense - Threat of biological terrorism has created a need for rapid testing devices to aid law enforcement officers who may come in contact with deadly biological agents. LOC and microfluidic technology will have great potential to be part of the ever-growing and highly lucrative military industry. A few companies and research centers include Acron Genomics and Sandia National Laboratories.

Forensics - The potential to test DNA at a crime scene in under several hours can greatly aid the investigation time and cost. The concept of implementing LOCs is currently under research across multiple universities. There has been substantial progress taking place in developing microfluidic chips for forensic science.

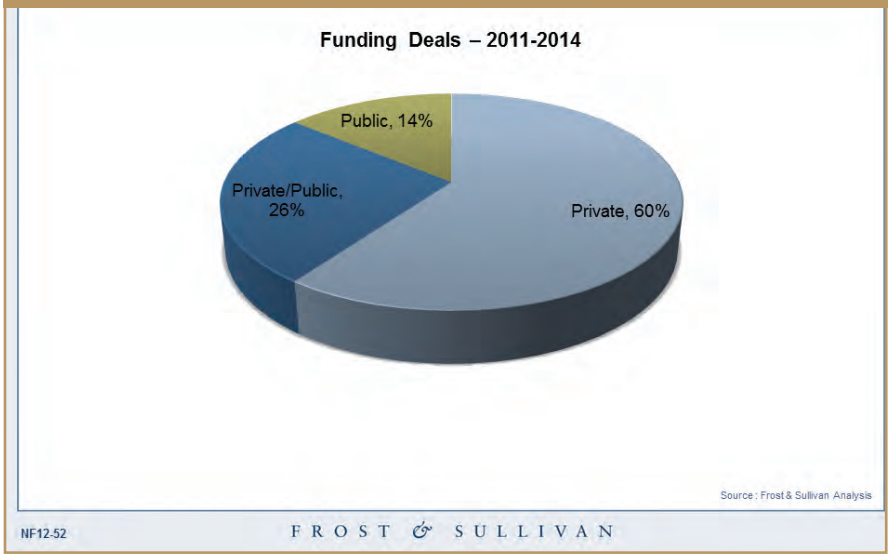
Given the wide range of application areas, it is important to note that the current demand for LOCs is created by the drug discovery and development and basic research across academics. Clinical use is the second most dominate market segment, with diagnostics leading the demand creation in this space.

TRENDS IN FUNDING

Development of these technologies requires funding support from venture capitals, government agencies (DARPA, NIH, US Army, NFSv and others), and private research funding organizations and charities. Reference Figure 2 for splits in funding patterns.

PathoGenetix received close to $10 million through Series C funding, raking a total current funding (as of press time) of $24 million. Hurel Corporation received close to $9.2 million through venture funding. DARPA and NIH have granted Wyss Institute $32 million toward research in developing human-on-a- chip technology to benefit pharmaceutical research. Acrongenomics has received multiple funds and grants, and Daktari Diagnostics received close to $9.1 million through public and private funding.

FIGURE 2



TECHNOLOGY DEVELOPERS

North America represents the largest number of technology developers across LOCs. European nations follow North America with the second highest number of companies working in the LOC space. Amongst the Asian countries, India, Japan, and China are leading in technology development, specifically LOC-based POC. There is also an increasing number of university spin-offs entering the LOC space in the US, India, Germany, and Japan. Environmental monitoring and toxicity testing applications using LOC-based devices is growing in European countries as well. Patent applications are also prominent in countries with high-technology innovation.

TECHNOLOGY ADOPTERS

Among developing nations, some African countries have high adoption levels of LOC devices for diagnostics needs. Pharmaceutical and biotechnology adoption of LOC-based analytical devices is prominent in North America, Europe, and parts of Asia and Australia.

For developing countries, cost of technology development, infrastructure, awareness of technology benefits, and lack of research opportunities and funding are some of the major causes for these regions to lag behind in technology development.

The investment ecosystem has significantly changed in recent years due to a rapidly growing interest in organizations toward miniaturizing and developing remote diagnostic capabilities. Speculating a high return, investment bodies are highly interested in LOC and microfluidic chip-based technology, as the constant push in the direction of personalized medicine and better healthcare facilities results in a vital need for cost-effective solutions. ◆

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BIOGRAPHY

Divyaa Ravishankar is a Senior Industry Analyst for Frost & Sullivan's Life Sciences practice. She has diverse expertise within healthcare IT and life sciences with a focus on in vitro diagnostics. Her expertise constitutes of laboratory research, management consulting, and competitive intelligence. To supplement her expertise, she also has broad-ranging industry experience in varying sectors, where she has established long-standing working relationships with leading industry participants in areas like clinical diagnostics, pharmaceuticals, and biotechnology. Ms. Ravishankar, earned her MS (Hons.) in Biological Sciences from Birla Institute of Technology and Science, Pilani, India. For more information on Frost & Sullivan's global Life Sciences practice and offerings, please email kayla.belcher@frost.com or visit www.frost.com.

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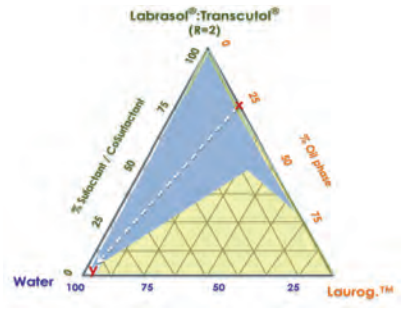
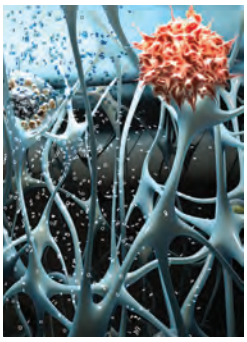
Formulation Development



Ternary diagramming is an indispensable tool for developing microemulsions and SMEDDS for topical or oral delivery of poorly soluble drugs. In this example, the blue zone represents unlimited number of formulations possible by simply varying combinations of three excipients. Point "X" for instance is SMEDDS containing 25% Lauroglycol™ +75% mixture of Labrasol®: Transcutol® (2:1). Continuously adding water to formulation "X", we would be following the dilution path along the white arrow. In other words, the formulation "X" may be diluted with no risk of phase separation as it will remain a nano-dispersion even at a very diluted state. Designing SMEDDS and Microemulsions binary and ternary diagramming is a Gattefossé expertise. For more information, please contact **jmusakhanian@gattefossecorp.com**.

Next-Generation Vaccines



Immunomic Therapeutics, Inc. (ITI) is a privately held clinical-stage biotechnology company headquartered in Hershey, PA, with lab facilities in Rockville, MD. ITI is developing next-generation vaccines based on the patented Lysosomal Associated Membrane Protein, or LAMP, Technology. The LAMP-Vax vaccine platform aims to increases the immune response to nucleic acid vaccines and simplify vaccine design and delivery, yielding safer, more cost-effective human and animal therapies. LAMP emerged from $20 million of NIH-funded research conducted by distinguished scientist Dr. Tom August at the Johns Hopkins University School of Medicine. ITI has the exclusive worldwide license to the LAMP technology patent estate and is commercializing ground-breaking next-generation LAMP DNA vaccines, beginning with allergy, cancer, and infectious disease. For more information, contact Immunomic Therpeutics at (717) 327-1919 or visit **www.immunomix.com**.

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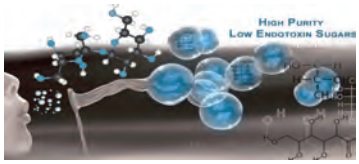

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The biologics manufacturing group at Althea has a highly experienced staff who work closely with the development group to ensure scalability to full cGMP production of drug substances. Our manufacturing facility is fully flexible and scalable with the ability to produce in 30L, 100L and 1,000L fermenters. As your program advances in the clinic, you can be assured that Althea will provide the capacity and quality to scale your process to larger product volume requirements without changing facilities Althea can take your product through clinical development and commercialization.

Drug Product, Aseptic Fill & Finish - Althea offers a unique range of aseptic filling in vials or prefilled syringes to address production needs that span from small scale early stage clinical products to larger scale commercial products. Our broad range of equipment and expertise paired with our flexibility and responsiveness, provide you with the capacity to advance your projects through all stages of clinical and commercial development. The formulation scientists at Althea have extensive knowledge and expertise in manufacturing a variety of complex formulations, including liposomes & nanoparticles, conjugates, crystallized proteins, adjuvants, and viscous products. Althea offers cGMP lyophilization services in conjunction with our Fill Finish capabilities. If you have an existing lyophilization process, we will work with you to transfer and adapt your lyophilization cycles to our equipment.

Analytical Services - Althea's analytical programs satisfy regulatory requirements and work to assure the success of the clinical program. Althea offers core services of method development and validation, product characterization, comparability studies, reference standard qualification and stability and release testing. The Analytical Scientists customize a phase-appropriate analytical program to the specific needs of your unique molecule to ensure a comprehensive understanding and characterization of the molecule for each stage of development and commercialization. With a thorough understanding of your molecule at an early stage in development, you can make process changes that are necessary for successful formulation, drug delivery, and fill finish. As your drug product advances through the clinic, Althea will design and execute analytical programs that support a full characterization of the drug product.

LET'S MAKE MIRACLES

WITH ALTHEA, YOU HAVE THE POWER TO MAKE.

You have the power to make a difference. To make new therapeutics that improve quality of life and inspire a healthier world. To do this, you need a manufacturing partner who embraces your every challenge as its own, who shares your unwavering tenacity and dedication from clinical studies through commercial success. That's The Power To Make.

CONTRACT MANUFACTURING:

- Development
- Drug Substance
- Drug Product

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ASHLAND®

Company Description

Ashland is a manufacturer and marketer of pharmaceutical grade excipients supported by global cGMP manufacturing and R&D with expertise in polymer science, formulation development, solid dispersions and bioavailability enhancement. Our global manufacturing sites are held to strict cGMP standards ensuring consistent production of high-quality products.

Ashland meets formulators' needs by providing an unparalleled range of excipients and technologies, as well as longstanding polymer expertise and technical support from benchtop to commercialization for oral solids, liquids, topical and parenteral dosage forms.

Research taking place at Ashland is the foundation of technical solutions that will address drug delivery challenges in the future.

Products, Services & Capabilities

Ashland's leading position in drug solubilization is underscored by its broad network of technical support and laboratories down to the regional level. The company operates pharmaceutical centers of excellence in Wilmington, Delaware (USA) and Hyderabad, India, and regional supporting laboratories in Düsseldorf, Germany; Istanbul, Turkey; São Paulo, Brazil; Buenos Aires, Argentina and Shanghai, China. Products include:

- Aqualon™ and Blanose™ sodium carboxymethylcellulose (CMC)
- Aqualon™ ethylcellulose (EC)
- AquaSolve™ hypromellose acetate succinate (HPMCAS)
- Aquarius™ film coating systems
- Benecel™ DC HPMC
- Benecel™ methylcellulose and hypromellose (HPMC)
- Benecel™ HPMC custom grades
- Cavamax*, Cavitron™ and Cavasol* cyclodextrins
- Klucel™ hydroxypropylcellulose (HPC)
- Natrosol™ hydroxyethylcellulose (HEC)
- Plasdone™ povidone and copovidone
- Polyplasdone™ crospovidone
- Pharmasolve™ N-methyl-2-pyrrolidone

www.ashland.com/pharmaceutical

Ashland Specialty Ingredients
8145 Blazer Drive
Wilmington, DE 19808
Tel: +1 877 546-2782

Company Background

A long and winding road has lead to a sharp focus on specialty chemicals.

What began as a small oil refinery in eastern Kentucky just over 90 years ago has grown into Ashland, Inc., one of the world's leading specialty chemical companies. From the beginning, the company's founder, Paul Blazer, instilled in Ashland employees a passion for hard work, integrity and results - qualities that endure today.

Markets Served

- Pharmaceutical
- Nutraceutical/Dietary Supplements
- Animal Health
- Personal Care/Skin Care

On September 30, 2014, Ashland Specialty Ingredients, a business unit of Ashland Inc., celebrated the opening of a state-of-the-art pharmaceutical center of excellence in Wilmington, Del. The new facility, which primarily focuses on drug development and bioavailability enhancement, expands Ashland's global network of pharmaceutical research and development centers. The facility also includes formulation development and supports early stage clinical trials spray drying and extrusion processes.

BAXTER HEALTHCARE CORPORATION
One Baxter Parkway
Deerfield, IL 60015
US: 1.800.422.9837 International: 1.847.948.4779
E: biopharmasolutions@baxter.com
Website: www.baxterbiopharmasolutions.com

Baxter's BioPharma Solutions business collaborates with pharmaceutical companies to support commercialization objectives for their molecules. As a parenterals specialist with over 80 years of expertise, BioPharma Solutions offers contract manufacturing form/fill/finish services and solutions for injectables designed to meet complex and traditional sterile manufacturing challenges. As a global injectables specialist, we can help solve unique challenges with confidence of delivery, service and integrity.

Industry Leader with Global Presence/Expansive Network/Manufacturing Resources

With manufacturing operations in 28 countries, Baxter's global presence provides opportunities for unique manufacturing collaborations to provide the most value for our clients. The power of an extensive network lies in the coordination of, and efficiencies resulting from, a systemic approach to cGMP manufacturing. Baxter's versatile, worldwide manufacturing resources gives you the assurance needed to meet global market demand, from form/fill/finish of small molecule parenterals to production of cytotoxics and biologics, such as monoclonal antibodies and recombinant proteins.

Meeting Parenteral Manufacturing Challenges

Parenteral manufacturing can be a complex process. Cytotoxics, antibody-drug conjugates (ADCs), highly potent compounds, biologics, and lyophilized products require specialized understanding and our dedicated facility in Halle/Westfalen, Germany, has over 60 years of experience handling cytotoxics and highly potent drug manufacturing. Our Round Lake, IL, facility is the world's leading provider of manufacturer prepared IV solutions and offers best-in-class aseptic solution manufacturing, and our Bloomington, IN, facility is one of the largest contract manufacturers of sterile products in North America.

Areas of Expertise

As a parenterals specialist, BioPharma Solutions offers unique delivery systems and a variety of manufacturing solutions to meet complex and traditional manufacturing challenges.

- **Sterile Manufacturing Solutions**
  - Prefilled Syringes
  - Liquid Vials
  - Lyophilized Vials
  - Cartridges
  - Diluents for Reconstitution
  - Ampoules
  - Powder Filled Vials
  - Sterile Crystallization
- **Parenteral Delivery Systems**
  - Frozen Premix System
  - Liquid Premix System
  - BIO-SET Luer System
- **Drug Categories**
  - Small Molecules
  - Biologics
  - Vaccines
  - Cytotoxics
  - Antibody-Drug Conjugates (ADCs)
  - Highly Potent Compounds
  - Cephalosporins / Penicillins

We Take Partnering Seriously

We have alliances with over 60 pharmaceutical clients and realize that having successful collaborations are critical in this extremely competitive environment. BioPharma Solutions has developed strong organizational capabilities to help ensure that we provide the value you deserve and expect.

Baxter

ViE
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AWARDS
• Winner 2015, 2012-2010

- Small Molecules
- Biologics
- Cytotoxics
- ADCs
- Highly Potent

- Prefilled Syringe Filling
- Liquid and Lyo Vial Filling
- Cartridge Filling
- Diluents for Reconstitution
- Proprietary Flexible Bags
- And more...

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for Specialized Sterile Injectables

Whether you face formulation challenges, clinical supply hurdles, surges in demand due to market fluctuations, risk mitigation concerns, or patent expiry challenges, we offer tailored, versatile solutions–*and over 80 years of parenteral experience*–to help you achieve your commercialization objectives.

Ultimately, our goal is to make you feel confident and secure in choosing BioPharma Solutions as your CMO–assisting you to avoid the unexpected and guiding you through marketplace complexities to help you achieve the full potential for your molecule.

To contact us or learn more, visit:
baxterbiopharmasolutions.com

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InformEx is uniquely positioned to help chemical companies transform into science and technology companies. For over thirty years, the innovation-focused show has built a global network of customers, suppliers and colleagues in some of the most rapidly growing chemical markets, including medical devices, pharmaceuticals, biopharma and biologics.

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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 solubility and stability limitations in drugs. Seven FDA-approved, CAPTISOL-enabled® medications are marketed by: Pfizer, Zoetis, Baxter Healthcare and Onyx Pharmaceuticals (a subsidiary of Amgen Inc.). CAPTISOL® also has agreements in place with a number of pharmaceutical companies worldwide with CAPTISOL-enabled® product candidates. Routes of administration investigated include parenteral, oral, ophthalmic,nasal, topical, 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 initially filed with the FDA and is updated annually.

This regulatory safety data package, which continues to grow and now includes more than 70 volumes, supports the use of CAPTISOL® in parenteral formulations as well as substantial registration support for other routes of delivery. In addition, in 2007, a Type IV DMF was filed and contains extensive Chemistry Manufacturing and Controls (CMC) information regarding our GMP-manufactured CAPTISOL®. 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. 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 gram sample, please visit www.captisol.com and click on "TRY CAPTISOL" button located on the Home Page within the beaker photo.

Catalent®

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Website: www.catalent.com

Catalyst + Talent. Our name combines these ideas. Catalent is the global leader in development solutions and advanced drug delivery technologies, providing world-wide clinical and commercial supply capabilities for drugs, biologics, consumer health and animal health products. With more than 80 years serving the industry, we have proven expertise in bringing more customer products to market faster, enhancing product performance and ensuring reliable product supply.

We serve thousands of innovators, both established and emerging, in over 80 countries, including 82 of the top 100 pharmaceutical and 40 of the top 50 biotech marketers. Our team of over 1,000 talented scientists has supported nearly half of innovative drug and biologic approvals since 2005, and we have more than 500 active development programs for new customer products. We have 20 development teams in 10 markets. From 31 global sites, Catalent serves over 1,000 customers and supplies around 70 billion doses annually. Our significant intellectual property includes over 1,400 patents and patent applications.

Whether you are looking for a single, tailored solution, or multiple answers throughout your product's lifecycle, we can improve the total value of your treatments – from discovery to market and beyond.

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

Development

With our broad range of expert services – including analytical, biologics, pre-formulation and formulation – we drive faster, more efficient development timelines and produce better products. With innovative SMARTag™ technology to advance ADC development and our robust GPEx® mammalian cell line engineering technology, large molecule drugs can be accelerated from discovery to clinic, and our new OptiForm™ Solution Suite ensures maximum API optimization. With our deep expertise and our extensive formulation capabilities across a wide range of dose forms, we can solve even the most complex bioavailability, solubility, and permeability challenges.

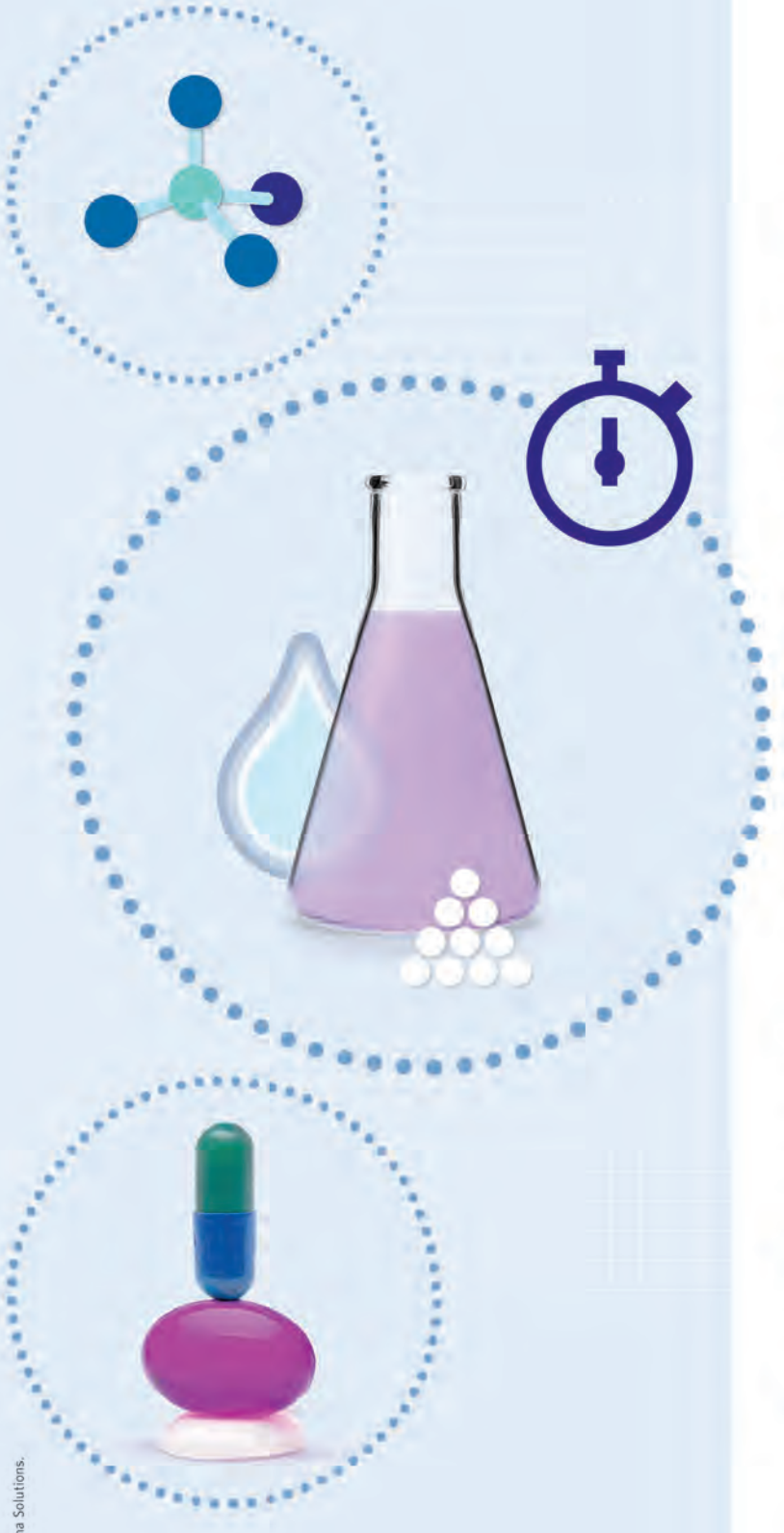
Delivery

We are a world leader in drug delivery solutions with a proven track record of helping our customers create better treatments by boosting bioavailability, solubility, and permeability; improving ease and route of administration; and increasing patient compliance. Our unique delivery technologies – including RP Scherer softgel and OptiShell™ capsules, Zydis® fast-dissolve, controlled release, including OSDrC® OptiDose® flexible dose delivery and OptiMelt® hot melt extrusion, as well as inhaled and injectable dose forms – improve how products work in and for patients.

Supply

We reliably supply our customers through operational and quality excellence, and we have regulatory inspection results exceeding the industry average. As a seamless extension of your supply chain, we offer global, integrated manufacturing and packaging solutions to take your product from design to clinical trial to plant and to pharmacy. We manufacture oral, sterile and inhaled dose forms and produce biologics for pre-clinical and clinical studies.

Catalent®



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Pharmaceutical formulators need to achieve API solubility and stability to create market leading products with maximum efficacy, quality, and performance. Superior quality and ultrahigh purity make Croda a supplier of choice in the global pharmaceutical market. Our proprietary manufacturing and purification technology yields high-quality products that meet the exacting requirements of international Pharmacopoeia. Offering one of the widest ranges of chemical specialties, surfactants, and high-purity lipids available to the pharmaceutical industry, with products manufactured at multiple sites throughout the world, Croda provides a complete range of products for topical dosage forms as well as multi-compendial solvents and surfactants suitable for parenteral, oral, ophthalmic, nasal, vaginal, and suppository formulations.

Technical Services

Croda's ongoing investment in GMP API technologies and R&D ensures the continual delivery of exceptional ingredients and the development of new specialty products to answer current and future health and wellness needs. To achieve products with such superior quality and purity, Croda developed a proprietary process called Super Refining™. This process physically removes impurities from pharmaceutical excipients and nutritional oils without altering their fundamental structure in any way.

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

Insulet Delivery Systems Group

Insulet Corporation

INSULET CORPORATION
600 Technology Park Drive, Suite 200
Billerica, MA 01821
P: (978) 600-7011 E: drugdelivery@insulet.com
Website: www.omnipoddelivery.com

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 helps offer improved adherence, outcomes, and differentiation throughout a drug'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.

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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 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.

Medical Innovation From Start To Finish

EG GILERO

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About Exostar

Exostar's cloud-based solutions help companies in regulated industries mitigate risk and solve identity and access challenges. Nearly 125,000 organizations worldwide leverage Exostar to help them collaborate securely, efficiently, and compliantly with their partners and suppliers. By offering connect-once, single sign-on access, Exostar strengthens security, reduces expenditures, and raises productivity so customers can better meet contractual, regulatory, and time-to-market objectives.

Founded in 2000, we envision a world in which innovation does not stall because of security, but is progressed further for it. In the past 15 years, our combination of technical advancement, customer intimacy and a commitment to maintaining security at all levels has made Exostar the preferred collaboration solution provider across the life sciences industry. As part of Merck's Global Health Initiative, we aspire to seed collaboration and make the world a more secure connected place to share ideas, develop solutions, increase productivity and lower costs.

Featured Products

Secure Access Manager: Turnkey cloud-based identity and access management solution developed for the life sciences industry to allow partners to collaborate more efficiently and securely.

Partner Information Manager: Continuous risk management solution that empowers organizations to manage, assess, measure, and mitigate risk across their multi-tier partner and supplier network.

Secure Share: A multi-tenant collaboration application that provides federated, claims-aware authentication supporting single sign-on access. The platform supports file sharing, joint research, clinical trial development, net meetings and partner access.

Federated Identity Service: Fully-managed, public key infrastructure (PKI) service for the issuance and maintenance of digital certificates, including Safe-BioPharma certified SHA-2 compliant certificates.

Collaboration Risk Management

Providing identity and access solutions for collaboration and cybersecurity risk management, throughout your value chain

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P: (201) 265-4800
Website: www.gattefosse.com/en/gattefosse-usa
Contact: jmusakhanian@gattefossecorp.com

Group Profile

The Gattefossé Group provides innovative excipients and drug delivery solutions to health industries worldwide. With a service and distribution network that spans more than 60 countries, the Gattefossé Group ensures responsiveness to the pharmaceutical industry's needs from both regional and global perspectives.

Gattefossé in the USA

At Gattefossé Corporation, our highly trained group of professionals and technical staff strive to meet and surpass customer expectations. To further our services, we have rolled out plans for significant expansion of the North American operations which include opening of an application lab in 2016 and additions to technical staff.

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.

Products

Lipid excipients and related drug delivery systems are the core specialties of Gattefossé. We transform oleo-chemicals into sophisticated functional excipients of pharmaceutical quality for a wide range of applications in oral, topical, transdermal, nasal, injectable, rectal, and vaginal routes of administration. The product offer consists of liquid and solid solubilizers, emulsifiers, bioavailability enhancers, sustained release matrix formers, penetration enhancers, and processing aids for tablets and capsules.

Formulation Development Insight

We publish and share our core knowledge in the form of scientific articles and formulation guidelines on many topics such as solid dispersions by extrusion, adsorption, granulation, and coating techniques; micro / nano emulsions; binary and ternary systems for SMEDDS; supersaturable systems; lipolysis testing set-ups; solid lipid nanoparticles; and sustained release matrices. Guidance documents for excipient selection and formulation design for preclinical as well as late development stages are available.

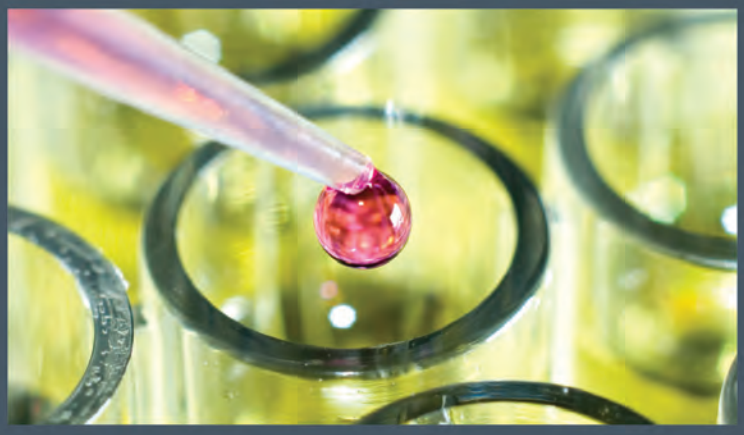
Safety, Regulatory & Quality Support

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 in turn 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.

Excipients for Smart Drug Delivery Solutions



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Year Founded: 1992

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 23 years.

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 m^2 to 4.5 m^2
- 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 565 diverse products:

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

Development Sciences

Development Sciences lab focuses on formulation through product characterization. The Process Lab provides capacity for small/medium scale lyophilization. Filtration, filling, stoppering and loading 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 unique requirements. The CMA includes an aseptic suite featuring unique disposable negative pressure isolators for containment/isolation technology, 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

LTI provides Development and Clinical Trial Material Manufacturing to more than 403 biopharmaceutical companies spanning virtual, small, large and multi-national companies. Gaining an international reputation, projects are with clients in US, Canada, Mexico, Eastern and Western Europe, Australia and Japan.

Benefit from the focused expertise gained from working on 565 diverse products, collaborating with over 403 companies over 23years.

Talk with the people who can provide you the right answers

Development Sciences Clinical Manufacturing Technical Services

LYOPHILIZATION TECHNOLOGY, INC.
Integrating Science and Technology

30 INDIAN DRIVE • IVYLAND, PA 18974 USA
PHONE +1 (215) 396-8373 • FAX +1 (215) 396-8375
www.lyotechnology.com • inquiry@lyo-t.com

Metrics Contract Services
1240 Sugg Parkway
Greenville, NC 27834
P: (252) 752-3800 E: thomas.salus@maynepharma.com
Website: www.metricsinc.com

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.

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.

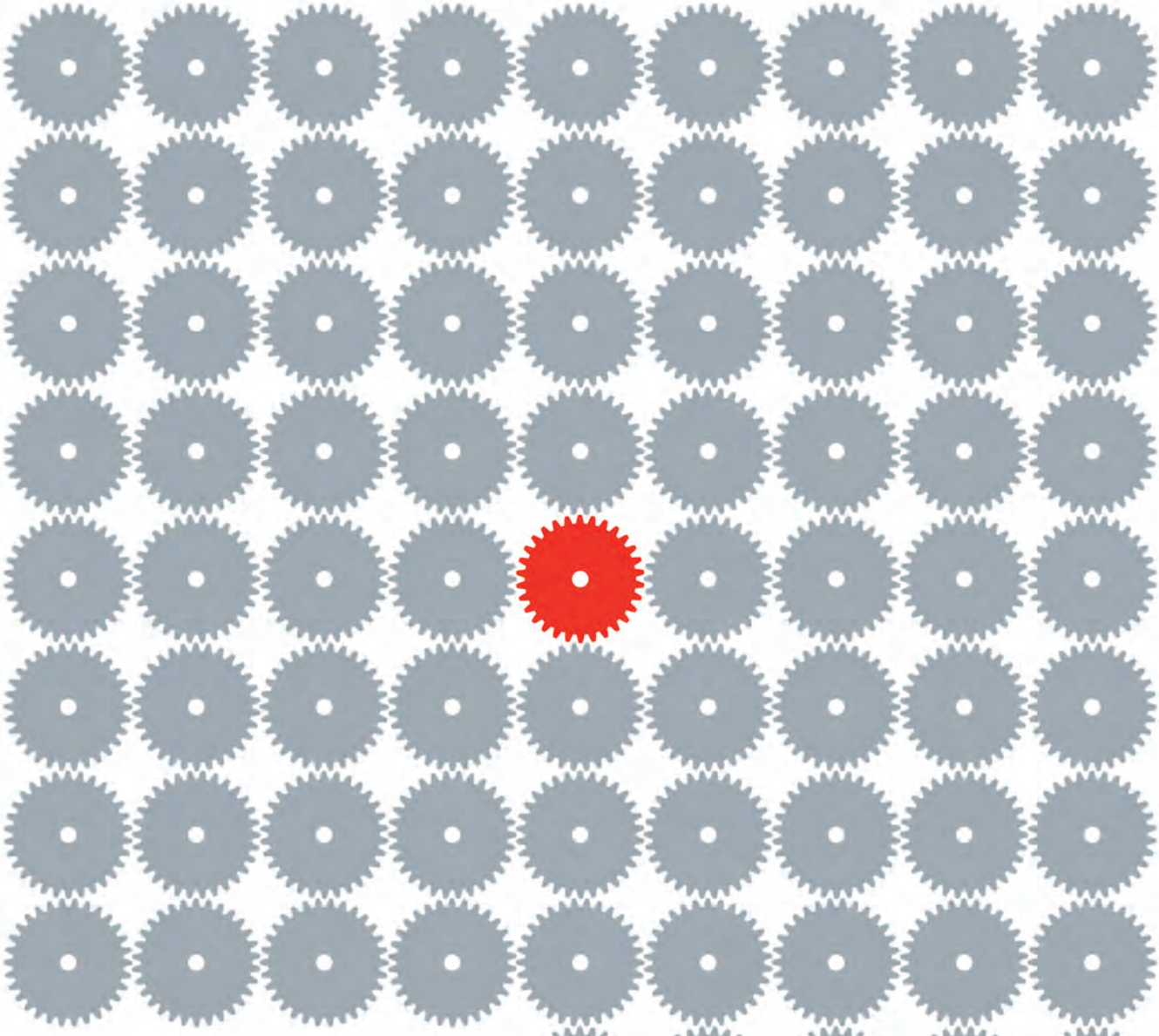
Commercial Manufacturing

Seven manufacturing and packaging rooms for Phase III clinical trial or commercial manufacturing of solid oral dose formulations, including DEA II-V controlled products. Full analytical support is available – release testing, stability, microbiology testing, and custom analytical development and validation.

Concept to Commercialization

The parent company of Metrics Contract Services, Mayne Pharma, is investing $65 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.



When you bring your development project to Metrics Contract Services, you're bringing it to a finely-tuned team of scientists and technicians committed to delivering quality, on-time results. And at the center of every team is an experienced, veteran scientist backed by a robust complement of analytical chemists, all moving your project forward day by day. A well-oiled system that keeps bottlenecks and backups at bay, and timelines always top of mind.

Smart science. Even smarter client service. How a great CDMO should work.

At Metrics, There's Always A Great Scientist Keeping Your Project Team Moving.

Pharmaceutical Development • Analytical Testing • CTM Manufacturing • Potent Products

Metrics Contract Services, Greenville, NC, 252-752-3800, www.metricsinc.com

metrics contract services

MULTISORB Technologies

MULTISORB TECHNOLOGIES
325 Harlem Road
Buffalo, NY 14224
T: 716-824-8900 E: info@multisorb.com
Website: www.multisorb.com

*Success Through Efficiency*SM

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.

MULTISORB Technologies

Drive Your Success Through Sorbent Efficiency

With an industry leading **output efficiency of >99.997%**, our MultiSystem™ approach provides the lowest total cost of ownership for sorbent dispensing applications.

Our *Success through Efficiency*℠ program offers everything you need to help efficiently Identify, Select and Dispense the optimal sorbent while meeting your objectives for cost and speed. We'll help you gain efficiency, reliability and quality. Contact us today.

www.multisorb.com

MINNESOTA RUBBER & PLASTICS
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P: (952) 927-1400 Fax: (952) 927-1470
E: webmaster@mnrubber.com

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.

We Turn Ideas Into Results.

Advanced Material Technologies

Every day at Minnesota Rubber and Plastics we produce high tolerance medical components and assemblies for the most demanding applications. Our experience in advanced material formulation enables us to be compliant with FDA, ISO 10993 and ISO 13485 to meet your unique product requirements. Our over 60 year history in the design and manufacture of complex devices makes us the preferred partner for industry leaders throughout the world. The next time your component or assembly project seems impossible, there's no one better to partner with than Minnesota Rubber and Plastics. We'll make your tough application a reality.

For a project evaluation call : 952-927-1400.
Email requests to medical1@mnrubber.com
Download our complete literature and design guide at mnrubber.com/medical1

Minnesota Rubber & Plastics
Quadion LLC

Leader in Advanced Material Technologies

PharmaCircle™

Global Data and Analytics for Pharmaceutical, Biotechnology and Drug Delivery Professionals

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Tel. 1-800-439-5130 (in the U.S. & Canada)
+1-760-436-1199 (International)
www.pharmacircle.com

PharmaCircle is a leading provider of global data and analysis on the pharmaceutical, biotechnology and drug delivery technology industries. PharmaCircle's premier database connects product and pipeline information for drugs and biologics with formulation and component details, and provides due diligence level data on over 5,400 drug delivery technologies and devices. Multi-parameter searches can be performed across hundreds of variables including phase, mechanism of action, molecule type, therapeutic category, route, dosage form and administration.

Drug label comparison tools, full-text regulatory document search capabilities, development summaries, deals/venture capital transactions tracking, and company profiles help to further streamline research. PharmaCircle's enterprise solution includes our premier database, concierge-level support and expert insight.

PharmaCircle's Pharmaceutical Science and R&D Searchable Databases and Analyses Include:

DD Technology (>5,400 Technologies)	Products & Pipeline (>100,000 Products)	Drug Delivery Analyses (49 Topics)
FDA Excipient (>12,800 Excipients)	Molecule (>35,000 Molecules)	How Supplied Injectable (>7,600 Products)
Drug Delivery Reviews (46 Topics)	FDA Package (>200,000 Packages)	How Supplied Non-Injectable (>18,000 Products)
Drug Delivery Patent (>84,000 Patents)	Clinical Trials (>200,000 Clinical Trials)	FDA Dissolution Methods (~1,100 Records)

Plus, over 30 business intelligence and regulatory search modules.

PharmaCircle

The Difference is in the Details

FORMULATION

What started as the premier drug delivery and formulation database continues to be the best. And now all of this information is connected with pipeline and product information that formulation specialists need.

RESEARCH

With more than three dozen separate data modules and three unique search engines, PharmaCircle provides researchers with the tools to find the information they need, online and at their fingertips.

DEVELOPMENT

Clinical trials, development costs and more are provided by the PharmaCircle database modules and search engines. While some online resources can let you search with one or two parameters, PharmaCircle let's you look at the situation with multiple parameters for a whole new perspective.

REGULATORY

PharmaCircle has recompiled, and translated as necessary, regulatory databases from around the world and added on whole new search engines that let you get information and do the type of analysis you didn't think possible.

The Details Make All the Difference

It's one thing to know what products are on the market and in development. It's another to have detailed information about their form, formulation and use.

PharmaCircle provides the type of details that can't be found elsewhere:

- dosage form, shape, color, coating and excipient amounts
- dosing quantities and frequency, injections sites and volumes
- packaging, kit components, storage conditions and shelf life

And this is only the information that would be of particular interest to Pharmaceutical Science professionals. The same level of detail is provided for development, regulatory and business professionals.

Navigating PharmaCircle is as simple as using the single field Global Search interface or as detailed as a multi-parameter search using the Flexible Search interface with nested Boolean operators. The Panoramic Search engine permits multiparameter searches with a graphical output that can be easily distilled to provide the results you are looking for. The Detailed Search provides similarly detailed searches with tabular output. Drug label comparison tools and full-text document search capabilities help to further streamline research.

All search engines provide options to display the results in table and chart formats that can be downloaded in Word, Excel and Adobe Acrobat formats.

Interested in learning more or a demo? Give us a call or drop us an email.

PharmaCircle™

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E: contact@pharmacircle.com
www.pharmacircle.com

Pfanstiehl, Inc.
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T: (847) 623-0370 Toll Free (800) 383-0126
F: (847) 623-9173 E: cs@pfanstiehl.com
Website: www.pfanstiehl.com

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.

REVOX Sterilization Solutions
14605 28th Avenue North
Minneapolis, MN 55447
Toll-Free: (855) 473-8690 E: info@revoxsterilization.com
Website: www.revoxsterilization.com
Twitter: @REVOXSterile

ROOM TEMPERATURE STERILIZATION

The REVOX® Sterilization Solutions process uses a patented, room-temperature peracetic acid (PAA) vaporized 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 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.

SUPERIOR MATERIALS COMPATIBILITY

Until now, you've been limited by traditional sterilization methods that constrain your choice of materials and overall product design. REVOX changes that. With true room- temperature processing and demonstrated superior compatibility across a wider range of materials, you have more options to innovate more efficiently. 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 changes that. REVOX enables scalable in-line sterilization, which finally allows you to integrate sterilization into a lean manufacturing process. It speeds up production and gives you a substantial competitive edge. Think of it as JUST-IN-TIME™ sterilization. It's your time. Make the most of it.

Teleflex VaxINator™

Intranasal Drug Delivery Device

TELEFLEX MEDICAL INCORPORATED
2917 Weck Drive
Research Triangle Park, NC 27709
T: USA: (866) 246-6990 International: +1 919 544-8000
E: vaxinator@teleflex.com
Website: www.vaxinator.com

Teleflex VaxINator™

The Teleflex VaxINator™ is Teleflex's leading intranasal drug delivery device available exclusively to drug researchers, pharmaceutical and vaccine companies developing intranasal drugs and vaccines. Utilising the same atomization technology as LMA MAD Nasal™ (www.lmaco.com), Teleflex VaxINator is a reliable and economical option when choosing a delivery device for intranasal drugs.

The Teleflex VaxINator is an easy-to-use and cost-effective solution for intranasal drug delivery. Applications include intranasal vaccines, pain medications, anaesthetics, antimicrobial, and many other possibilities.

The design of the Teleflex VaxINator enables a standardized position in the nasal passageway that directs the spray plume through the nasal valve where the broad angle of the plume allows for broad deposition across the nasal mucosa. The atomizer output is a fine mist of particles 30-100 microns in size. The range of droplet size delivered by the device allows for particulate deposition across both anterior and posterior areas of the nasal cavity to facilitate rapid absorption.

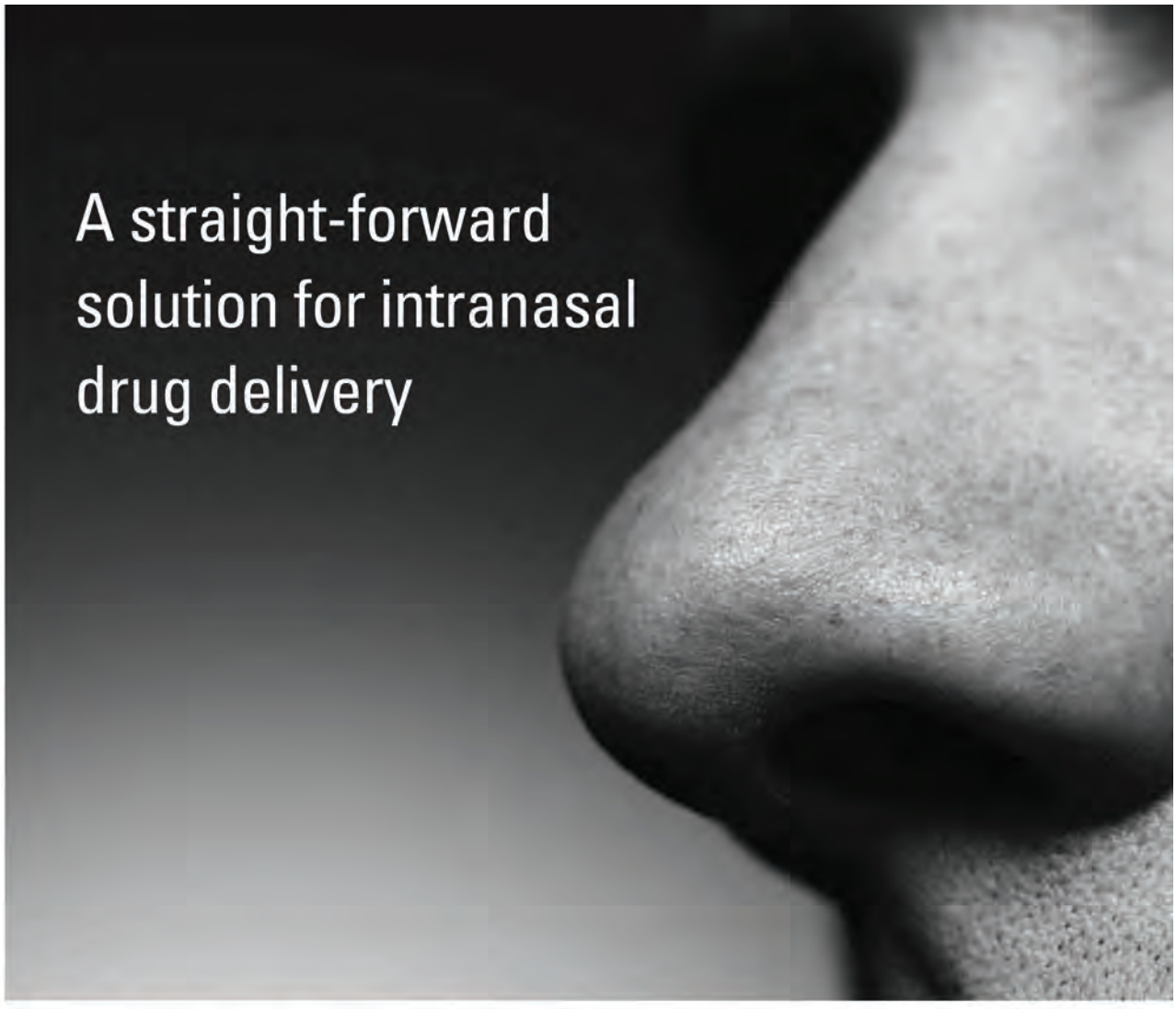
The Teleflex VaxINator is made from radiation-stable medical-grade polycarbonate material and is compliant with USP Class VI and ISO 10993 requirements. In addition to the provision of the nasal atomizer, Teleflex also provides a range of accessories, for example, dose dividers, auto-disable syringes etc., to meet our customers' needs. These can be provided in bulk non-sterile format or in sterile kits.

The simplicity and elegance of the Teleflex VaxINator design enable high-quality, high-volume manufacturing, ensuring that it is both a reliable and cost- effective OEM option. Teleflex offers full service OEM capabilities, which combine high-quality products, extensive design, engineering and manufacturing experience, attentive service, and expert support.

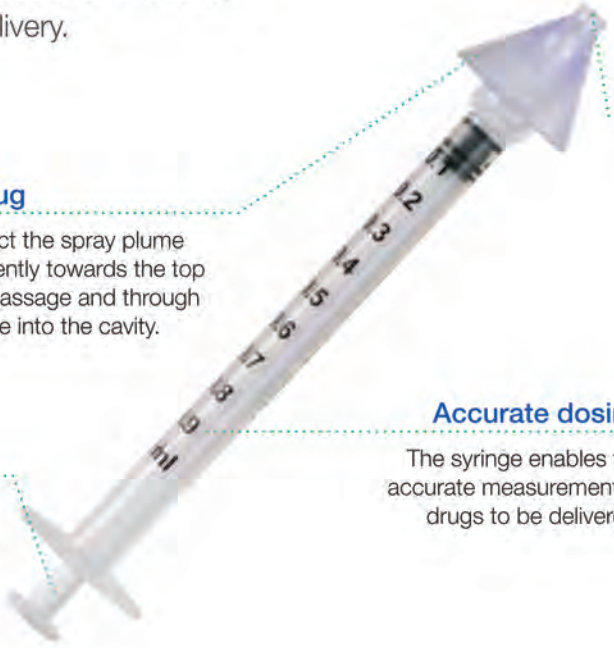
Our in-house team of design engineers is available to work on any customisation requirements you may have, and we will project manage the entire process, including initial design, prototyping, inventory management, demand planning, and logistics.

We are committed to investing significant time and effort into demand planning and risk mitigation to ensure high-quality product supply when you need it and where you need it.

A straight-forward solution for intranasal drug delivery



The Teleflex VaxINator™ is used for effective, easy-to-use nasal drug delivery.



Atomization spray

The spray atomizes drugs into a fine mist of particles 30-100 microns in size.

Conical plug

An aid to direct the spray plume more consistently towards the top of the nasal passage and through the nasal valve into the cavity.

Accurate dosing

The syringe enables the accurate measurement of drugs to be delivered.

Pressure

High applied pressure ensures that drugs are atomized into a fine mist of particles through the tip of the plug.

Patent pending.

For use with drugs approved for nasal delivery.

30-0344 Rev. 09/13.

Phone +353 (0)1 896 4961 **Email** vaxinator@teleflex.com www.vaxinator.com

Teleflex

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Somerset, NJ 08873
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F: (732) 302-3083
Website: www.terumo-gps.com

About Terumo

Terumo Corporation 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.

Global Pharmaceutical Solutions

Terumo Global 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.

TERUMO

Polymer (COP) Pre-Fillable Syringes

Integrated Luer Lock and Staked Needle

- 1ml & 2.25ml Luer Lock compliant with ISO 594-1/594-2
- 1 ml long staked needle: Silicone oil-free autoinjector functionality
- Minimizing extractables and leachables
- Uncompromised Quality and Regulatory Affairs support

PLAJEX™
Ready-To-Fill Plastic Syringes

Prototypes available on request

www.terumo-gps.com

UNILIFE®

Deliver Brilliance

A BROAD, MARKET-DRIVEN PORTFOLIO TO ENHANCE AND DIFFERENTIATE YOUR INJECTABLE THERAPIES

WEARABLE INJECTORS

- For the self-injection of drugs with dose volumes 1mL or larger and / or extended delivery profiles
- Prefilled, pre-assembled and supplied ready for self-injection
- No terminal sterilization required
- Three simple steps: peel, stick, click
- Standard materials and filling
- Bluetooth LE connectivity
- Fully customizable to target drug

PATCH PUMPS FOR INSULIN

- The first prefilled, pre-assembled instant patch pump for insulin
- Preset basal rate for continuous subcutaneous insulin infusion
- On-demand single-button bolus
- No ancillary equipment required
- Compact size for comfortable, discreet multi-day wear
- No priming required by patients
- Bluetooth LE connectivity

AUTO INJECTORS

- A unique range of disposable and smart reusable systems
- Designed for Unifill syringes
- True end-of-dose indicators
- Needle-free disposal
- Intuitive steps of use
- Fully customizable
- Customization options include Bluetooth LE connectivity, drug warming and touchscreen display

PREFILLED SYRINGES

- For all prefilled drugs, biologics and vaccines
- Fully integrated, automatic, user-controlled needle retraction directly from the body to prevent needlestick injury risk
- Utilizes standard materials, filling and packaging systems
- Ergonomic, customizable design
- Intuitive steps of use

RECONSTITUTION SYSTEMS

- Suitable for liquid-liquid or liquid dry drug combinations
- Single and double barrel syringe options available
- One-step reconstitution
- Ventless, orientation-free
- Intuitive steps of use
- Utilizes standard materials, filling and packaging systems

OCULAR AND NOVEL SYSTEMS

- A unique range of products specifically designed to administer drugs into the eye or other organs
- Technologies include microliter doses, drug depots and combination therapies
- Accurate, precise delivery
- Intuitive steps of use
- Highly customizable

250 Cross Farm Lane, York, PA 17406, USA
T: 1 717 384 3400 W: www.unilife.com E: info@unilife.com

UNILIFE®

Deliver Brilliance

Imperium™ instant patch pump for insulin

Delivering the therapeutic advantages of an insulin pump, with the simplicity and cost of an insulin pen.

Low dose volume wearable injector

Enhance patient comfort, reduce pain and speed drug warming for biologics 1 mL or less in dose volume

Precision-Therapy™ wearable injector

Optimized for biologics with long-duration injections where specific dose delivery volume determines clinical outcomes.

Flex-Therapy™ wearable injector

Optimized for biologics with long-duration injections where specific dose delivery rate determines clinical outcomes.

Prefilled and Pre-Assembled

Industry standard filling and materials with no terminal sterilization required.

Minimal Steps to Therapy

Supplied to patients ready for use in a fully integrated system. Just peel, stick and click.

Fully Customizable

A highly adaptive platform to address the specific needs of each drug and indication.

Discreet, Extended Wear

A compact, user-centric design for optimal comfort, convenience and discretion during wear.

Smart-Enabled Connectivity

Bluetooth LE connectivity with smartphones to enable patient reminders and status updates.

E: info@unilife.com W: www.unilife.com

UPM Pharmaceuticals, Inc.
501 5th Street
Bristol, TN 37620
T: (423) 989-7057 E: mschiesz@upm-inc.com
Web: www.upm-inc.com

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.

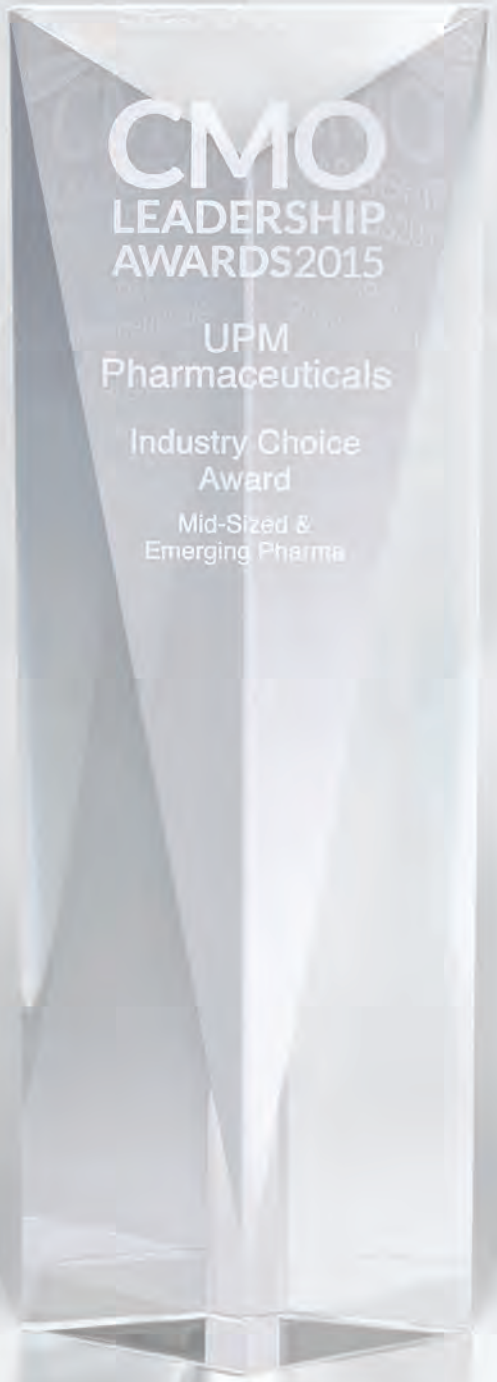
UPM is characterized by its strict sense of quality, timeliness, sound scientific fundamentals, and affordability with which we complete all our projects. We focus on drug development and manufacturing for dosages with oral routes of administration in solid forms, such as capsules and tablets, and semi-solid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

UPM Pharmaceuticals®
Formulating Your Future™



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UPM Pharmaceuticals is proud to have won the 2015 Industry Choice Award, singling out our company as the #1 choice CMO for mid-sized and emerging pharma. Thank you to all the industry buyers that voted for us.

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Company Profile

West Pharmaceutical Services, Inc.
530 Herman O. West Drive
Exton, PA 19341-0645
T: US: (610) 594-2900 or
(800) 345-9800, EU: +45 7561 6000
Website: www.westpharma.com

By Your Side

Every day, injectable drugs improve the lives of millions of patients around the world. And every day, West is working by your side to design and manufacture drug packaging and delivery systems that will bring your drugs from concept to the patient more efficiently, reliably, and safely. West understands your challenges and helps with solutions every step of the way. We provide cutting-edge production technologies, an unmatched expertise in global regulatory compliance, and an ever-growing knowledge base of pharmaceutical drug product testing, development, packaging, and delivery. Whether your focus is on one piece of the process or you want an end-to-end solution, West is by your side for a healthier world.

NovaPure® Components

Patient safety influenced the design process for NovaPure stoppers and syringe plungers from start to finish. West developed NovaPure components by incorporating Quality-by-Design principles to help ensure enhanced component reliability and an unrivaled level of quality. With NovaPure components, pharmaceutical manufacturers can help ensure a safe injectable drug product for patients.

West Analytical Services

West's wealth of knowledge and experience in laboratory testing and regulatory guidances helps customers mitigate the risks associated with package selection and keeps product development moving forward. West is a trusted source for extractables and leachables testing, container closure integrity testing, compendial testing, and more.

Injection System Platform Technologies

West's platform technologies provide solutions for self-injected drugs covering a range of dose volumes and drug viscosities. West's platform technologies include the ConfiDose®, SmartDose®, and SelfDose™ injector technology platforms.[1]

Needle Safety Systems

West's needle safety systems have been designed to provide protection for healthcare workers and patients against accidental needlestick injuries. In extreme cases, needlestick injuries can lead to serious problems, such as hepatitis B and C and HIV. West's platform technologies include NovaGuard® SA, NovaGuard LP and eris™.

Daikyo Crystal Zenith® Ready-to-Use Solutions

The Crystal Zenith polymer is break-resistant and highly transparent. Available in a variety of vials, containers, and syringes, a solution using Crystal Zenith polymer is the answer to drug product life-cycle management.

Administration Systems

West develops and manufactures safety and administration systems for the reconstitution, mixing, transfer, and administration of injectable drugs. Mixing and transfer systems include MixJect®, Mix2Vial®, Vial2Bag®, and vial adapters.

[1]For investigational use only by our pharmaceutical and biotechnology development partners. These platforms are intended to be used as an integrated system with drug filling and final assembly completed by the pharmaceutical/biotechnology company.

West markets the NovaGuard® SA platform technology as an integrated system. Final assembly is performed by the pharmaceutical manufacturer.

West

By your side
for a healthier world™

Empower your patients

The SmartDose® electronic wearable injector combined with the HealthPrize adherence program makes for a powerful combination. The SmartDose injector helps your patients leave the treatment center behind, making self-administration at home simple and easy. And while at home, HealthPrize helps your patients stay on track with their therapeutic routine, through rewards-based patient education and adherence tracking.

HealthPrize

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West seeks partners for its SmartDose electronic wearable injector technology platform. This platform is intended to be used as an integrated system with drug filling and final assembly completed by the pharmaceutical/biotechnology company. The SmartDose system, HealthPrize platform integration is for conceptual purposes only.

For complete contact information please visit www.westpharma.com.

#9368 1015

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Contact: Sharon Burgess, Senior Vice President

THE EVOLUTION OF SUITE SCIENCE

Xcelience's Suite of Services is evolving to meet the current and future demands of our clients. With the integration of Powdersize, our suite of services has expanded to maximize the potential for API success by creating a smooth client experience into formulation development. Services include milling, micronization, preformulation, analytical services, formulation development, cGMP manufacturing, small-scale commercial manufacturing, and global clinical supplies packaging and logistics. Xcelience takes pride in delivering the highest standards in science and service with an emphasis on quality, cost, and speed. Since 1997, Xcelience has been providing comprehensive drug product development and contract manufacturing solutions to our global pharmaceutical and biotech customers. Xcelience continues to expand capabilities to help our clients achieve their goals, deepen our client relationships, and increase our efficiencies. For the past 2 years, we have added global clinical supplies packaging and logistics, small-scale commercial manufacturing, and Powdersize's milling and micronization to our service offerings. We listen to our clients' needs and deliver solutions.

SERVICES & CAPABILITIES

Preformulation
- Polymorph Identification
- Salt Screen/Selection
- X-Ray Diffraction
- Thermal Evaluation
- Vapor Sorption Analysis
- Powder Characterization
- Laser Diffraction Particle Size Analysis
- pKa Determination
- Log P/Log D Determination
- pH Solubility Profiles
- Intrinsic Dissolution
- FT-IR & UV/Visible Spectroscopy

Analytical Services
- Method Development, Qualification & Validation
- Method Transfer
- Raw Material Testing
- Release Testing

Formulation Development
- Tablets
- Capsules
- Semi-Solids
- Oral Liquid Dosage Forms

cGMP Manufacturing & Small-Scale Commercial Manufacturing
- Compressed Tablets
- Sustained Release & Non-Functional Coating
- Reference Product Blinding
- API in Capsule
- Liquid in Hard Capsule
- Semi-Solids
- Non-Sterile Liquids

Global Clinical Supplies Packaging
- Bottling
- Blister Packaging
- Labeling for a Multiple Variety of Primary Containers
- Kit Assembly Including Ancillary Supplies
- Blister Card/Wallet Sealing
- Comparator Sourcing
- Cold Room Labeling
- Clinical Labeling

Global Clinical Supplies Distribution & Logistics
- Global Distribution
- Cold Chain Capabilities (2°C-8°C, -20°C,Dry Ice)
- Point of Distribution (POD) Labeling and Distribution
- Clinical Supply Storage
- Retains
- Returns
- Reconciliation
- Destruction

FACILITES

Xcelience currently has 5 locations. In the US, the Savarese headquarters houses preformulation and analytical services and formulation development. The West Laurel Street location contains all cGMP manufacturing and small-scale commercial manufacturing. The West Grace Street facility is dedicated to global clinical supplies primary and secondary packaging. The Johns Road facility is used for global clinical supplies distribution and logistical services. In the UK, Xcelience has a facility in Burton-on-Trent, near Birmingham that provides secondary packaging, labeling, and distribution throughout Europe. Specific Xcelience facilities have DEA I-V, low humidity conditions, and refrigerated/freezer operations and handling available.


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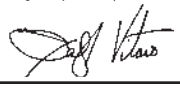

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