Drug Development & Delivery

November/December 2012 Vol 12 No 9 www.drug-dev.com

Market Trends, Advancements & Improved Methods

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

Winny Tan, PhD
Trends in Outsourcing Pharmaceutical Development & Innovation

Dave Miller, PhD
KinetiSol®: A New Processing Paradigm for Amorphous Solid Dispersion Systems

Kevin Menard, PhD
Improvements in Characterization of Pharmaceuticals: Fast Scanning Rate DSC Methods

IN THIS ISSUE

INTERVIEW WITH NOVOZYMES BIOPHARMA'S CUSTOMER SOLUTIONS MANAGER

MARK PERKINS

Outsourcing Trends 14
Winny Tan, PhD
Jennifer Brice

Global Biosimilars Market 18
Deborah Toscano
Jennifer Brice

Drug Delivery Advancements 22
Deborah Toscano

The Future of DPIs 26
Geralt Williams, PhD

Amorphous Solid Dispersions 30
Dave Miller, PhD
James DiNunzio, PhD

Pharmaceutical Characterization 40
Brian Lynch, MBA
Philip Song, MSc

Company Profiles 51

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Table Of Contents

14 **Industry Trends: Outsourcing Pharmaceutical Development & Innovation**

Frost & Sullivan Analysts Winny Tan, PhD, and Jennifer Brice highlight two dynamic pharmaceutical service segments, CROs and IVD manufacturers, and how they are evolving to meet the growing preclinical and clinical trial needs of pharmaceutical companies. They also discuss open innovation models for outsourcing the earliest stage of drug discovery.

18 **Global Biosimilars Market: Large Opportunity Due to Patent Expiries of Blockbuster Biologics**

Frost & Sullivan Analysts Jennifer Brice and Deborah Toscano observe how the arrival of biosimilars, or highly similar copies of biopharmaceutical products, to the US market is imminent, and although they have been available elsewhere for several years, physicians and other key stakeholders in the US have only recently begun to anticipate their arrival.

22 **Recent Advancements in Drug Delivery: Novel Formulations & Technologies Offer Improved Treatment Options**

Debbie Toscano, Senior Industry Analyst, Frost & Sullivan, highlights a few recent innovative approaches to drug delivery with a focus on some of the therapeutic areas most relevant to the current pharmaceuticals market.

30 **KinetiSol®: A New Processing Paradigm for Amorphous Solid Dispersion Systems**

Dave A. Miller, PhD; James C. DiNunzio, PhD; Justin R. Hughey, PhD; Robert O. Williams III, PhD; and James W. McGinity, PhD; review how a novel fusion-based process for the production of amorphous solid dispersion systems has recently been adapted to pharmaceutical processing and is providing novel solutions for difficult-to-process compounds.

40 **Improvements in Characterization of Pharmaceuticals: Fast Scanning Rate DSC Methods**

Kevin P. Menard, PhD, MBA, says fast scanning rate DSC represents a recent and underutilized technique for the characterization of pharmaceutical materials and highlights several of the more common applications.

44 **The Impact of Packaging at the Clinical Interface of Vaccine, Healthcare Worker & Patient**

Brian Lynch, MBA; and Philip Song, MSc; indicate further adoption of vaccines packaged in PFS is expected to continue, for both new and currently marketed vaccines, particularly as clinicians and vaccine enterprise stakeholders look more closely at the implication of packaging at the user interface and understand the benefits PFS offer in terms of greater efficiency and advancing best care.

48 **Novozymes Biopharma: Improving Drug Safety & Stability With Recombinant Human Albumin**

Drug Development Executive: Mark Perkins, Customer Solution Manager at Novozymes Biopharma, discusses how the company is improving the formulation of many new drugs and offering customers new ways of achieving a competitive advantage.

51 **Company Profiles**

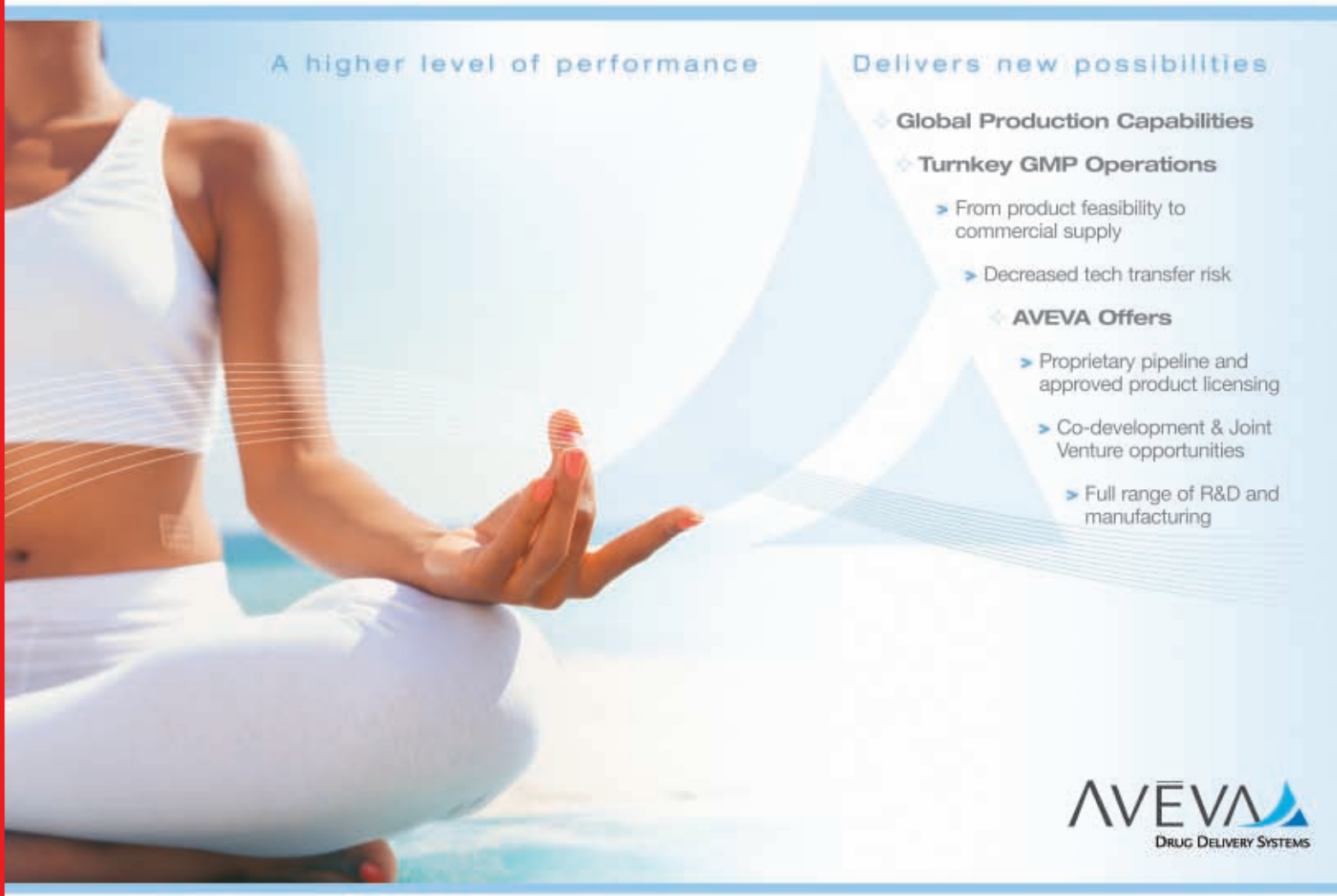
For each participating company, this section presents a special 2-page spread featuring their core technologies, capabilities, products, and services.

Departments

Market News & Trends 8

Advanced Delivery Devices 26
The Future of DPIs: Aligning Design With Market Demands

TRANSDERMAL TRANSCENDENCE



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Novartis Expects 14 New Blockbusters

Novartis recently provided an update on its leading Research and Development (R&D) pipeline and plans for turning these assets into commercial success to provide the basis for continued growth of the group through 2017. Continuing R&D productivity in the Pharmaceuticals Division has fueled an industry-leading pipeline with 139 projects in clinical development with more than 73 New Molecular Entities (NMEs) across a multitude of disease areas. Highlights include RLX030 and LCZ696 in heart failure as well as AIN457 in psoriasis and multiple sclerosis. In addition, the company will showcase a comprehensive early and late-stage pipeline of novel oncology compounds.

Novartis Group continues to lead the industry with 56 new approvals in the US, Europe, Japan, and China since 2007. In 2012 alone, the Pharmaceuticals division has received nine approvals or positive recommendations to date. Novartis Pharmaceuticals has established a strong foundation for the company's ongoing growth based on currently marketed products. In addition for the next 12 months, Pharmaceuticals expects data read-out on 13 pivotal studies, 9 filings, and 7 regulatory decisions. For the following 13 to 24 months, strong pipeline newsflow is expected to continue with a further 11 pivotal trials read-out, 11 filings, and 10 regulatory decisions.

As evidenced by the recent launches of Afinitor, Seebri Breezhaler, Jakavi, and Signifor, Novartis has a proven track record of bringing innovative products to market. With the current marketed portfolio, Pharmaceuticals is expected to grow from the second half of next year despite loss of exclusivity on mature brands like Diovan, Zometa, and Aclasta.

In addition, Novartis is striving to increase efficiency and productivity to manage more projects while keeping costs at a stable level. Introducing novel technologies and methods reduce recruitment time and trial costs, while improving study quality and patient comfort and safety. These include mobile field monitoring, continuous manufacturing, and Telehealth. In addition, through a research initiative with Walgreens in the US, clinical trials will provide more real-world evidence and lower access barriers for participants.

Patheon to Acquire Banner Pharmacaps

Patheon Inc. recently announced it has entered into a definitive agreement with VION N.V. to acquire Banner Pharmacaps, a specialty pharmaceutical business dedicated to the research, development, and manufacturing of unique gelatin-based dosage forms.

Banner is the world's second largest pharmaceutical business focused on delivering proprietary softgel formulations for over-the-counter, prescription, and nutritional consumer products, with four manufacturing facilities, significant proprietary technologies and products, and leading positions in some of the industry's fastest-growing product categories. Banner is headquartered in High Point, NC, with additional research labs and manufacturing facilities in the Netherlands, Canada, and Mexico.

"The acquisition of Banner advances our strategic plan put in place in 2011, fully aligning with Patheon's intent to be the leader in oral dosage development and manufacturing services," said James C. Mullen, Patheon's Chief Executive Officer. "The transaction provides us with a well-balanced portfolio of proprietary products, state-of-the-art facilities with enhanced capabilities, as well as an expanded geographical presence. We believe our visibility within the industry will be further strengthened as we pass the $1-billion revenue mark."

The acquisition will be structured as a purchase of all of the shares of the entities through which Banner conducts its operations, for a purchase price of $255 million, subject to working capital and other adjustments. The acquisition is subject to applicable regulatory approvals and other customary terms and conditions, and is expected to close by the end of calendar 2012.

In support of the transaction, Patheon has received commitments for financing that will be applied to fund the acquisition and associated expenses, retire existing debt, and used for general corporate purposes. Such commitments are subject to customary terms and conditions.

Patheon Inc. is a leading global provider of contract development and manufacturing services to the global pharmaceutical industry. The company provides the highest quality products and services to approximately 300 of the world's leading pharmaceutical and biotechnology companies. Patheon's services range from preclinical development through commercial manufacturing of a full array of solid and sterile dosage forms.

Bayer & QIAGEN Partner on Cancer Companion Dx

QIAGEN and Bayer HealthCare recently announced a collaboration agreement for the development and commercialization of companion diagnostics paired with novel Bayer HealthCare drugs, initially to enhance the treatment of various solid tumors. Companion diagnostics are tests that unlock molecular information from each patient's tumor genome to guide treatment decisions with medications for cancers or other diseases. The parties will also collaborate on the development of novel technologies for patient profiling that may result in innovative research-use-only products for exploratory and translational medicine. Financial details were not disclosed.

The targeted companion diagnostics will be designed to run on the QIAsymphony family of automated instruments, which is transforming laboratory workflows and helping disseminate standardized, regulator-approved diagnostics.

"We are very pleased to partner with Bayer HealthCare in developing companion diagnostics to improve life for cancer patients. As healthcare providers increasingly select the right drugs based on each individual's genomic information, the treatment of cancer is undergoing a revolution," said Dr. Helge Lubenow, Senior Vice President Molecular Diagnostics Business Area and Member of the Executive Committee of QIAGEN. "The first collaborations for Bayer HealthCare and QIAGEN include companion diagnostics based on the identification of patients who may respond to therapies in clinically unmet disease classifications. Our agreement also lays the groundwork for a strong partnership in creating future companion diagnostics both inside and outside of oncology."

QIAGEN is a leading partner globally in developing and validating companion diagnostics to guide the selection of medicines in treating cancer and other diseases. In July 2012, QIAGEN received FDA approval for the therascreen KRAS RGQ PCR Kit as a companion diagnostic in patients with metastatic colorectal cancer.

Ziarco Pharma Acquires Pfizer Drugs, Secures Financing

Ziarco recently announced the closing of an initial $6-million tranche of Series A financing totalling $27 million. The round was led by Biotechnology Value Fund L.P, with participation by Pfizer Venture Investments.

Concurrent with the financing, Ziarco has entered into an agreement with Pfizer Inc. for the exclusive worldwide rights to commercialize a portfolio of clinical, preclinical, and research anti-inflammatory and anti-allergic assets. In return, Pfizer will receive equity as well as certain product-based milestone and royalty payments. Ziarco will use the proceeds of the financing to continue development of these assets and advance proprietary research.

"Ziarco was founded to address the significant need that still exists for new, more effective ways to treat disorders underpinned by inflammatory and allergic pathobiology. Each program in development at Ziarco has the potential to be a first-in-class therapeutic and because they target critical points within inflammatory and allergic pathways, they offer treatment options for diverse and difficult to manage diseases," said Dr. Mike Yeadon, CEO of Ziarco. "Not only are we very fortunate at such an early stage in the company's development to have licensed significant assets from Pfizer and secured funding from Biotechnology Venture Fund and Pfizer Venture Investments to progress development of these innovative therapeutic agents, but we have in place a highly experienced team which has deep knowledge of these programs and has the passion and expertise to deliver."

In addition to Dr. Yeadon, formerly Vice President and Chief Scientific Officer of Pfizer's Allergy and Respiratory Research Unit, Ziarco has been co-founded by three former Pfizer colleagues: Dr. Steve Liu, Vice President and Chief Scientific Officer; Dr. Lynn Purkins, Vice President and Head Clinical Development; and Dr. Arif Shivji, Vice President and Head Development Operations and Business Development.

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Sun Pharmaceutical to Purchase PhotoDynamic Company for $230 Million

Sun Pharmaceutical Industries Limited and DUSA Pharmaceuticals, Inc. recently announced they have entered into a definitive agreement under which Sun Pharma will acquire DUSA, a dermatology company focused on developing and marketing its Levulan (aminolevulinic acid HCl) photodynamic therapy platform.

DUSA's Levulan combination therapy is approved by the FDA for treatment of non-hyperkeratotic actinic keratoses or AKs of the face or scalp. Additionally, DUSA's BLU-U treatment has been approved by FDA for the treatment of moderate inflammatory acne vulgaris and general dermatological conditions. Levulan is manufactured by DUSA in its FDA-approved facility at Wilmington, MA.

Under the terms of the agreement, a 100% subsidiary of Sun Pharmaceutical Industries Ltd will commence a tender offer for all of the outstanding common stock of DUSA at a price of $8 per share in cash, a 38% premium to the closing price of DUSA's common stock on November 7, 2012. The transaction has a total cash value of approximately $230 million. The transaction has been unanimously approved by the boards of directors of both companies and DUSA's board has recommended that the company's shareholders tender their shares pursuant to the tender offer.

"DUSA has proven technical capabilities in photodynamic skin treatments, with USFDA approved manufacturing," said Dilip Shanghvi, Managing Director of the Company. "DUSA's business brings us an entry into dermatological treatment devices, where we see good growth opportunities."

Established in 1983, listed since 1994, and headquartered in India, Sun Pharma is an international, integrated, specialty pharmaceutical company. It manufactures and markets a large basket of pharmaceutical formulations as branded generics as well as generics in India, US, and several other markets across the world.

OUTSOURCING
DEVELOPMENT BRIEF

Industry Trends: Outsourcing Pharmaceutical Development & Innovation

By: Winny Tan, PhD and Jennifer Brice

INTRODUCTION

The successful business paradigm that began in the 1980s was the fully integrated pharmaceutical company (FIPCO) in which drug discovery research, development, manufacturing, and marketing were all conducted in-house. However, pharmaceutical companies are doing less of their drug R&D internally than they did decades ago. Today, the common business paradigm is the virtually integrated pharmaceutical company (VIPCO), or one that outsources much of drug development. Outsourcing is a necessary strategy to help offset the large number of blockbuster drugs coming off patent, competition from generics, and the low productivity of the pharmaceutical industry.

Contract research organizations (CROs), in vitro diagnostic (IVD) companies, clinical laboratories, regulatory consultants, and contract manufacturing organizations (CMOs) all support conventional pharmaceutical outsourcing needs. Pharmaceutical companies can engage external relationships upstream of these processes at the early drug discovery stage. Outsourcing drug discovery, or what the industry considers to be the innovation stage, has come about in the form of open innovation models in which pharmaceutical companies engage with government research institutes, universities, specialty pharmaceutical companies, and other external partners for the identification of promising drug candidates that match business interests. The following will highlight two dynamic pharmaceutical service segments: CROs and IVD manufacturers and how they are evolving to meet the growing preclinical and clinical trial needs of pharmaceutical companies. This brief will also discuss open innovation models for outsourcing the earliest stage of drug discovery.

A ROBUST & GROWING CRO MARKET REFLECTS THE HIGH DEGREE OF PHARMACEUTICAL OUTSOURCING

Contract research organizations (CROs) provide preclinical development and clinical trial services to the pharmaceutical industry. CROs have evolved from providing basic support services to providing a wide range of clinical, central laboratory, and analytical capabilities. Through CROs, pharmaceutical companies reduce operational costs by not having to maintain expensive R&D laboratories and scientists. CROs also bring strengths in patient recruitment for clinical trials and specialization in other disease areas. The CRO market is experiencing two-tiered growth from large pharmaceutical companies that want to lower fixed costs and specialty drug companies that lack of infrastructure. The $13.3-billion US CRO market is growing on average 8.4% annually through 2017.

Frost & Sullivan estimates that globally, CROs conduct more than two-thirds of the industry's Phase I through Phase III clinical trials. Market leaders in the US CRO market include Covance and Quintiles. The traditional sponsor-CRO relationship has shifted away from vendor-like and is moving toward long-term strategic alliances. With growing industry needs in emerging markets, comparative effectiveness research, and biosimilars trials, the CRO market opportunity is substantial - recent deals between Covance-Eli Lilly, Covance-Sanofi Adventis, and Pharmaceutical Product Development (PPD)-Merck alone are valued at more than $1 billion throughout the next 5 to 10 years. However, US CRO market growth is tempered by the risk of commoditization for services as well as competition from overseas.

COMPANION DIAGNOSTIC COMPANIES ARE LOOKING LIKE CROS

Advances in personalized medicine are presenting new opportunities for in vitro diagnostic (IVD) companies to capture business from pharmaceutical outsourcing. A large portion of drug

pipelines include highly targeted therapeutic compounds that require a diagnostic to identify eligible patients for the clinical trials. The drug and companion diagnostic are co-developed and co-approved to meet the FDA label requirement. It is rare for drug companies to have internal diagnostic development capabilities like Roche and Novartis. It is more common for the pharmaceutical company to work with an external companion diagnostic partner.

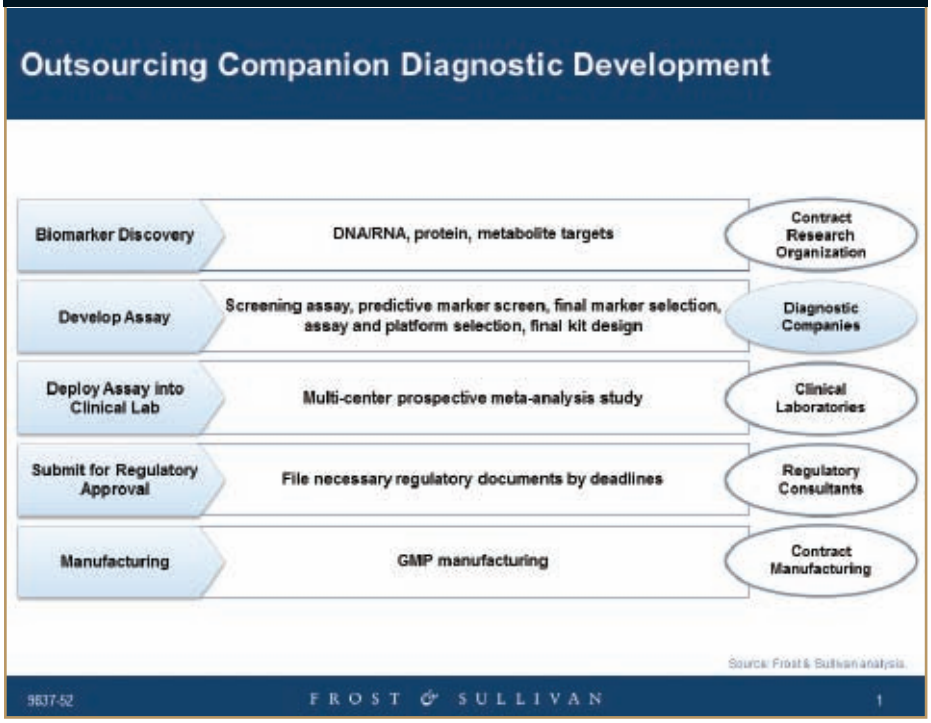
A recent Frost & Sullivan analysis studied the various co-development models. This type of partnership is a long-term commitment beginning pre-development and continuing post-market. Alignment challenges arise from fundamental differences in drug and diagnostic business models and also from the differences in development time frames and processes. Despite the challenges, outsourcing the companion diagnostic development makes sense while the diagnostic platforms are undergoing technological change. Using an external diagnostic partner provides the greatest flexibility in choosing the most appropriate diagnostic platform for selecting patients in the drug's clinical trials.

The recent co-approvals of Pfizer drug Xalkori with the Abbott Molecular ALK FISH test for non-small cell lung cancer and Roche drug Zelboraf with the Roche cobas® 4800 BRAF V600E mutation test for melanoma, both in 2011, achieved accelerated drug approval timelines of less than 6 years. These recent successes reinforce that the right companion diagnostic partner could offset diminishing industry returns by accelerating drug approval times.

OPEN INNOVATION IN THE PHARMACEUTICAL & BIOTECHNOLOGY INDUSTRY

"Open Innovation" was a concept first coined by Dr. Henry Chesbrough, a professor at Haas Business School at the University of California, Berkeley, and described in his book titled "Open Innovation: The New Imperative for Creating and Profiting from Technology" published in 2003. Open innovation in the drug industry is engagement with government research institutes, universities, specialty pharmaceutical companies, and other external partners for identifying promising drug candidates that match business interests. Numerous barriers to implementation exist within large pharmaceutical companies like competing priorities, a lack of infrastructure that facilitates collaboration, and overcoming established company cultures of relying on its own research versus sharing intellectual property (IP). All of the top 10 pharmaceutical companies have open innovation programs, and four case studies offer multiple strategies to facilitate collaboration, establish IP use terms, and allocate resources.

FIGURE 1

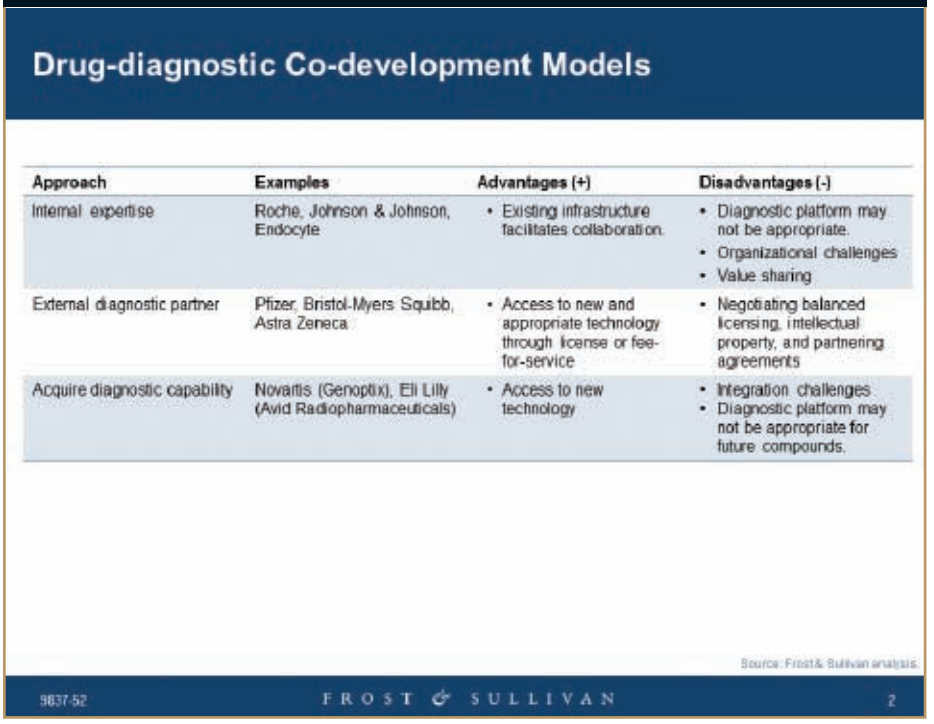


Pfizer launched its Centers for Therapeutic Innovation (CTI) in November 2010 to broaden its pipeline to treat disease with high unmet need. Core focus areas included oncology, primary care, specialty care, animal health, consumer healthcare, and nutrition. Each CTI is governed by a joint steering committee (JSC) composed of Pfizer staff and Academic Medical Center (AMC) representatives. The University of California, San Francisco, signed on as the first collaborator under the new program, and a number of additional academic centers from the East Coast have followed suit, each receiving initial investments of $100 million. In April 2012, Pfizer Canada announced its collaboration with the Center for Commercialization of Regenerative Medicine (CCRM) for regenerative medicine technologies for drug screening and therapeutic applications. Pfizer plans to expand this program into Europe and Asia in 2012 as well.

Novartis' Institutes for BioMedical Research (NIBR) was established in 2002 with locations in Boston, New Jersey, California, the UK, Switzerland, Italy, China, and Singapore. The NIBR institutes are staffed with scientists, chemists, disease area specialists, and clinicians. NIBR focuses on the pathway-disease connection in the areas of autoimmunity, transplantation, and inflammation, and cardiovascular, metabolic, gastrointestinal, infectious, musculoskeletal, neuroscience, oncology, ophthalmology, and respiratory diseases. The program delivered success with Ilaris (canakinumab), a monoclonal antibody approved in the US and the European Union in 2009 for the treatment of cryopyrin-associated periodic syndromes, including familial cold auto-inflammatory syndrome and Muckle-Wells syndrome. Furthermore, the NIBR has produced 12 positive proof-of-concept (POC) candidates in 2010. One POC study allowed researchers to link the interleukin-1 beta pathway imbalance with a number of diseases, including familial cold auto-inflammatory syndrome, Muckle-Wells syndrome, and neonatal-onset multisystem inflammatory disease.

GlaxoSmithKline (GSK) announced its open innovation strategy to fund new research in emerging markets in January 2010, outlining the following initiatives: establishing

FIGURE 2



Open Lab in Spain with $8-million seed funding for tropical disease research that would staff 60 scientists from around the world that includes establishing sustainable pricing models for advanced malaria vaccine development. The program allows free access to 13,500 compound prospects that may inhibit the malaria parasite. GSK also shares IP through a collaboration with BIO Ventures for Global Health (BVGH) to form a knowledge pool of new drugs to treat tropical diseases that was later joined by the Emory Institute for Drug Discovery (EIDD). EIDD is a collaboration with the South African firm, iThemba Pharmaceuticals, to develop treatments for tuberculosis, and a partnership with the World Intellectual Property Organization (WIPO).

Eli Lilly launched an open innovation drug discovery program subdivided into Phenotypic Drug Discovery Program (PD^2) and in vitro target-based assays ($TargetID^2$). Core focus areas include cancer, endocrine, cardiovascular, and neuroscience diseases. The program provides external investigators free access to a selected proprietary assay panel, use of Eli Lilly's state-of-the-art computational tools for structure design, confidential compound submission via web-based interface, and the chance for a potential agreement with Eli Lilly. Furthermore, Eli Lilly's program lets the IP rights remain with the investigator or institution.

The common theme across the open innovation models involves global external research alliances, the sharing of IP, and diseases for emerging markets. The significant investments available for promising candidates resulting from these programs reinforce that open innovation models are an important growth strategy for pharmaceutical companies moving forward.

WILL THE VIPCO ADDRESS THE CHALLENGES OF THE PHARMACEUTICAL INDUSTRY?

In the VIPCO model, pharmaceutical companies behave more like project and resource managers for the industry. In theory, this approach helps spread the high risk business of drug development across several cost-efficient projects in parallel. As the industry gains more experience in collaborative business partnerships, we may see more demanding pre-partnership negotiations. Future co-development agreements may evolve around risk sharing, access to intellectual property generated during development, and royalties from future pharmaceutical sales. The success of all external partnerships, no matter how innovative, will ultimately be measured against the effectiveness of increasing the industry productivity of safe and effective drugs. ◆

BIOGRAPHIES

Jennifer Brice currently serves as the Global Program Manager of the Life Sciences practice at Frost & Sullivan. Her industry expertise includes a strong network of key opinion leaders and senior executives within the pharmaceutical and biotechnology segments. Jennifer also has an experience base covering a broad range of sectors within the life sciences space, including infectious diseases, biosimilars, rheumatology/inflammatory diseases, and ophthalmology. She earned her Bachelors in Science from Ramapo College and her mini-MBA from Rutgers University.

Dr. Winny Tan is an Industry Analyst for Frost & Sullivan's Life Sciences practice with specialty areas in anatomic pathology, prenatal testing, clinical laboratory, and other IVD diagnostic markets. Dr. Tan's experience includes co-founding a personalized cancer diagnostic device company and evaluating medical technology start-ups for early stage funds. She earned her PhD in Biomedical Engineering from the University of California, Los Angeles.

MARKET BRIEF

Global Biosimilars Market: Large Opportunity Due to Patent Expiries of Blockbuster Biologics

By: Jennifer Brice, Frost & Sullivan Global Program Manager of Life Sciences, and Deborah Toscano, Frost & Sullivan Senior Industry Analyst, Life Sciences

INTRODUCTION

Biopharmaceuticals represent one of the most important innovations in medical history. However, these breakthrough therapies are extremely costly, owing to the magnitude of investment necessary in their discovery and development, driving a need for less-costly alternatives. While current regulations allow for the approval of generic copies of conventional pharmaceuticals at greatly reduced costs, until recently, there has not been the technology nor regulatory pathway with which to introduce lower-cost versions of biologics. The US Congress has recently enacted legislation to enable and encourage the introduction of biosimilars/follow-on biologics, paving the way into an untapped market.

In March 2010, the *Health Care Reform Bill*, formerly known as *The Patient Protection and Affordable Care Act of 2010*, became a law and included the *Biologics Price Competition and Innovation Act of 2009* (BPCIA). The BPCIA established an abbreviated regulatory pathway for the approval of biosimilars. The new legislation allows for two types of abbreviated applications:

- For products that are "biosimilar" to a reference biopharmaceutical.
- For products that are interchangeable with a reference biopharmaceutical.

The arrival of biosimilars, or highly similar copies of biopharmaceutical products, to the US market is imminent. Although they have been available elsewhere - including Europe and India - for several years, physicians and other key stakeholders in the US have only recently begun to anticipate their arrival.

GLOBAL MARKET OVERVIEW

The global biosimilars market was approximately $382 million in 2010 and is expected to continue to grow. The top three global biosimilars market participants contributed approximately 93% of the total market revenue. Sandoz International GmBH led the competition in 2010 with $185 million in revenue. Due to the company's strong investment in R&D and manufacturing capabilities, Sandoz has successfully been able to maintain its rank as the global biosimilars market leader. Teva Pharmaceuticals' acquisition of Ratiopharm in 2010 has allowed the company to stay ahead in the G-CSF segment, with global revenue of $112 million. Other players in the global biosimilars market include Hospira and Dr. Reddy's. Hospira has been active in the erythropoietin biosimilars segment and also announced its plans to enter into the filgrastim biosimilars market in 2010.

The global biosimilars market composition can be broken down into Europe, the US, and the Rest-of-World. The major part of the global biosimilars market is occupied by Europe, constituting nearly 45%, which is mainly due to the increase in approvals by the European regulatory

authorities.

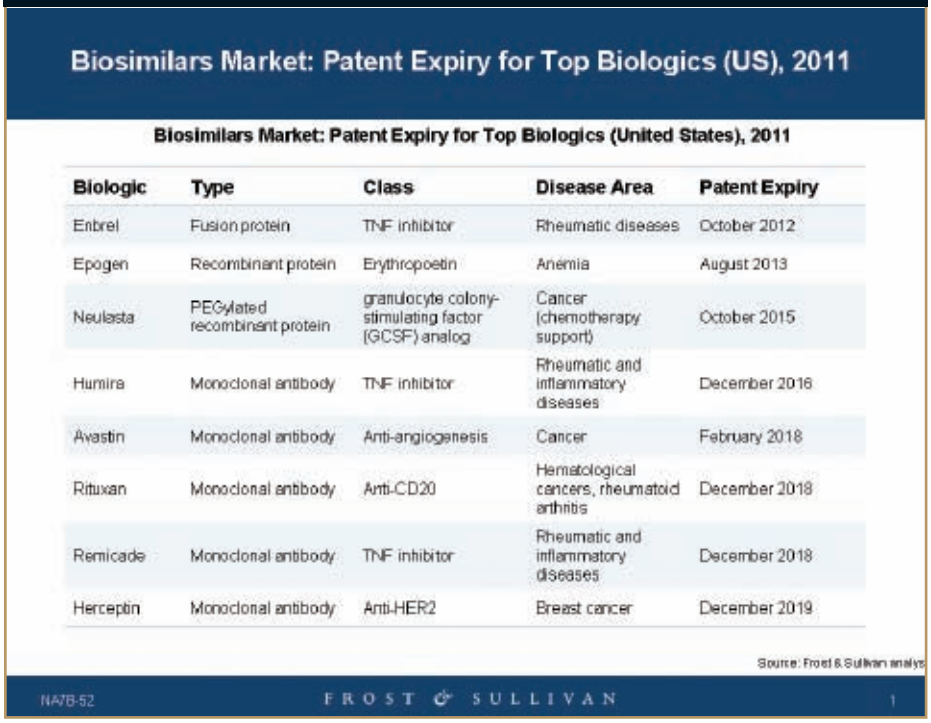
The European biosimilars market will continue to grow from approximately $172 million in 2010 to almost $4 billion in 2017 at a compound annual growth rate (CAGR) of 56.7%. Biosimilars that currently exist in the European marketplace consist of erythropoietins (erythropoietins alpha and zeta only), granulocyte colony-stimulating factors (GCSFs), and human growth hormones.

Among the European countries, Germany is the strongest market, constituting nearly 24% of the global portion of the biosimilars market. This is followed by the United Kingdom, France, Italy, and Spain, with nearly 5%, 4%, 3%, and 2%, respectively. The rest of the 7% is contributed by countries like Denmark, Sweden, Norway, Belgium, Netherlands, and others.

The Rest-of-World occupies 40% of the global biosimilars market. Among Asian countries, India has been growing stronger in biosimilars development.

The biosimilars market in the US is approximately 15% of the global biosimilars market, although there are very few products being approved due to the lack of guidelines by the US FDA. Biosimilars approved in the US include Sandoz's Omnitrope, a biosimilar version of the Pfizer's recombinant human somatropin, Genotropin. Although Omnitrope is a biosimilar, approval was only granted in light of the fact that human growth hormone is a relatively simple and well characterized molecule, unlike many of the commonly used biologics, such as monoclonal antibodies.

FIGURE 1



The US FDA is still in the process of establishing clear guidance for the industry for the submission of marketing applications for biosimilars. On February 9, 2012, the FDA issued highly anticipated draft guidance outlining the basic requirements for biosimilar applications. The basic data requirements will be similar to those for approval of conventional generics, including sufficient analytical data, animal data including a toxicology profile, and at least one clinical trial demonstrating safety, pharmacokinetics, pharmacodynamics, immunogenicity, and efficacy in the intended indication. However, the clinical trial requirements needed for biosimilars will be much more rigorous than those needed for conventional generics, and it is this requirement that will have the greatest influence on the development costs and thus the final discount versus the reference product. While the industry still awaits final guidance, the FDA has emphasized a few points:

- The FDA will consider each application on a case-by-case basis, in light of the extreme complexity of biopharmaceuticals, and they will consider the "totality of the evidence."
- The FDA has emphasized the importance of extensive analytical data demonstrating similarity between the biosimilar and the reference product, as they do not wish to encourage unnecessary animal and human testing.
- The FDA encourages companies to continually meet with the FDA throughout the development process.

An important feature of the draft guidance is the allowance of a different delivery system than the reference product, opening the door for a biosimilar to differentiate with an improved delivery system, such as an advanced injection pen. A downside for biosimilar manufacturers is that it currently appears that the FDA will likely not approve biosimilars as "interchangeable" with the reference product, meaning that the pharmacist cannot automatically substitute a biosimilar for the branded product; it will have to be intentionally prescribed. The current thinking is that the technology does not yet exist to produce an exact copy of a biologic molecule.

GLOBAL MARKET FORECAST

As a result of major patent expirations for blockbuster biologics, the global biosimilars market is bound to grow, especially with the new legislations for biosimilars in the US, Japan, and other Asian countries.

Frost & Sullivan estimates the global biosimilars market is expected to reach $12.5 billion by 2017 at a CAGR of 64.5%. However, the biosimilars market is complex, with many factors, such as the following, that may affect its potential:

- Products with different administration routes may gain favor over less-desirable methods.
- Biosimilars for chronic diseases may be viewed differently than biosimilars that are used only once.
- Doctors may be more willing or less willing to prescribe biosimilars depending upon the indication (cancer versus immunological disorders).
- Doctors may not be willing to switch patients who are already using biopharmaceuticals to a biosimilar.
- Doctors may prescribe biosimilars only to new patients.
- While generic medicines will produce significant cost savings, biosimilars are not expected to save much.

SUMMARY

The overall adoption of biosimilars can be expected to experience widespread uptake in light of anticipated access to comparable therapeutic options at a lower cost versus high-cost biologics. Main factors with the potential to influence the rate and extent of uptake include cost, safety, and efficacy data, including testing in specific patient populations, and reputation of the manufacturer.

Potential skepticism may be overcome with the help of convincing non-inferiority clinical data for products from reputable companies highly experienced with biologics. Educational programs deemed to be unbiased that convey this data could help increase awareness and boost physician confidence in biosimilar products. ◆

BIOGRAPHIES

Jennifer Brice currently serves as Global Program Manager, Life Sciences at Frost & Sullivan in North America, Mountain View, where she devises strategies and leverage resources to deliver projects in an efficient manner from initial design to implementation. Ms. Brice has a strong ability to train, advise, and supervise analysts on project material and provide strategies for collecting primary and secondary information, as well as manages and executes quality control activities to ensure client deliverables meet top standards. Her industry expertise includes a strong network of key opinion leaders and senior executives within the pharmaceutical/biotech segments and an experience base covering a broad range of sectors within the life sciences space, including infectious diseases, biosimilars, rheumatology/inflammatory diseases, and ophthalmology. Previous experience includes both operational and project management roles in a consulting firm focused on the life sciences industry and Senior Analyst/Operations Manager at CIS Life Sciences/Business Research Group (now Prescient Life Sciences) in Mt. Olive, NJ. Ms. Brice earned her BSc from Ramapo College and her mini-MBA from Rutgers University.

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MARKET BRIEF

Recent Advancements in Drug Delivery: Novel Formulations & Technologies Offer Improved Treatment Options

By: Debbie Toscano, Senior Industry Analyst, Frost & Sullivan

INTRODUCTION

The pharmaceutical and biotechnology industries have come a long way when it comes to advancements in drug discovery. New "druggable" targets and mechanistic approaches to treating even complex diseases are constantly discovered and optimized, generating a rich pipeline and continuous supply of fresh therapeutics for difficult diseases, such as autoimmune inflammatory disorders (for example, rheumatoid arthritis, inflammatory bowel disease), cancer, hepatitis C, and other infectious diseases, as well as neurological conditions, such as multiple sclerosis, to name a few.

However, developing a safe and effective drug is only part of the picture - perfecting the delivery of that drug into the patient is also a significant aspect of the total pharmacotherapeutic regimen. It is generally accepted by the pharmaceutical industry that the oral route of delivery is most preferred by the patient. However, this is not always possible or optimal due to formulation challenges or specifics of the particular indication being treated. For example, biologicals, such as vaccines or therapeutic antibodies, typically must be injected directly into the bloodstream because oral ingestion would result in the destruction of the fragile protein composition. Also, orally administered drugs tend to be distributed systemically, whereas the diseased portion of the body may be localized to a single organ or tissue. Thus, oral administration and systemic distribution may result in unnecessary exposure to the drug and unwanted side effects that could potentially be avoided with targeted drug delivery and isolation at the source of disease. Therefore, pharmaceutical and drug delivery companies are thinking outside of the box to address the issues associated with sub-optimal drug delivery.

This market brief will discuss a few recent innovative approaches to drug delivery with a focus on some of the therapeutic areas most relevant to the current pharmaceuticals market.

RECENT DEVELOPMENTS IN INJECTABLE DRUG DELIVERY

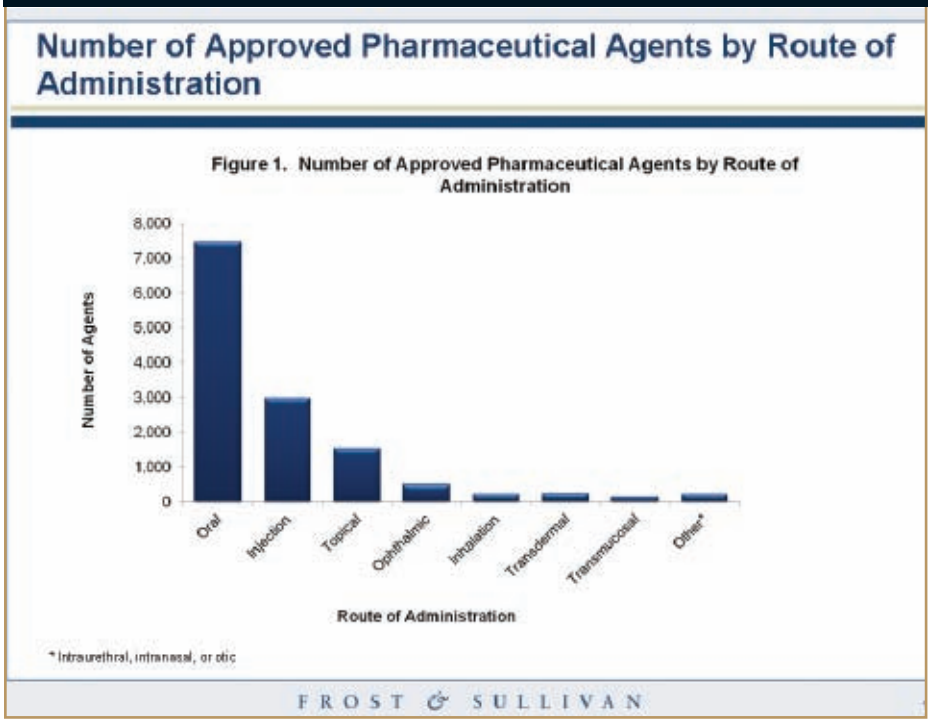
As seen in Figure 1, oral administration tops the list of approved pharmaceuticals, with approximately 7,468 total products on the market or approved for marketing. However, when looking at the development pipeline, injectable agents outnumber oral agents, with approximately 3,327 injectable agents in development versus 2,686 oral agents (Figure 2), as a result of the booming biotech industry. Medical advances, such as in biologicals, have revolutionized pharmacotherapy for complex diseases, such as rheumatoid arthritis, Crohn's disease, diabetes, and multiple sclerosis. Products like tumor necrosis factor (TNF) inhibitors for rheumatoid arthritis or glucagon-like peptide-1 (GLP-1) analogues for diabetes offer patients true disease-modifying benefits as opposed to simply treating the symptoms, and these benefits generally outweigh the discomfort associated with injection. All other things being equal, subcutaneous is generally the preferred injectable route as it can be easily performed by the patient at home using delivery devices, such as autoinjectors or pen injectors. However, even with the most sophisticated pen injectors, it still may be considered an unpleasant experience by many patients.

Tailoring the delivery of injectable drugs is mainly dependant on the specifics of two parameters: formulation and device. When injection is a necessity, new delivery

technologies can improve the experience in several ways. For example, formulation enhancements can reduce the frequency of administration, reduce the volume needed for each injection, or reduce side effects associated with the formulation, such as immunogenicity. Delivery device improvements, such as a smaller needle or autoinjectors that improve ease of self-injection, can significantly improve the patient experience. Although the pharmaceutical industry makes many attempts to move away from injectable administration, injectable drugs continue to fill the development pipeline as demonstrated in Figures 2 and 3.

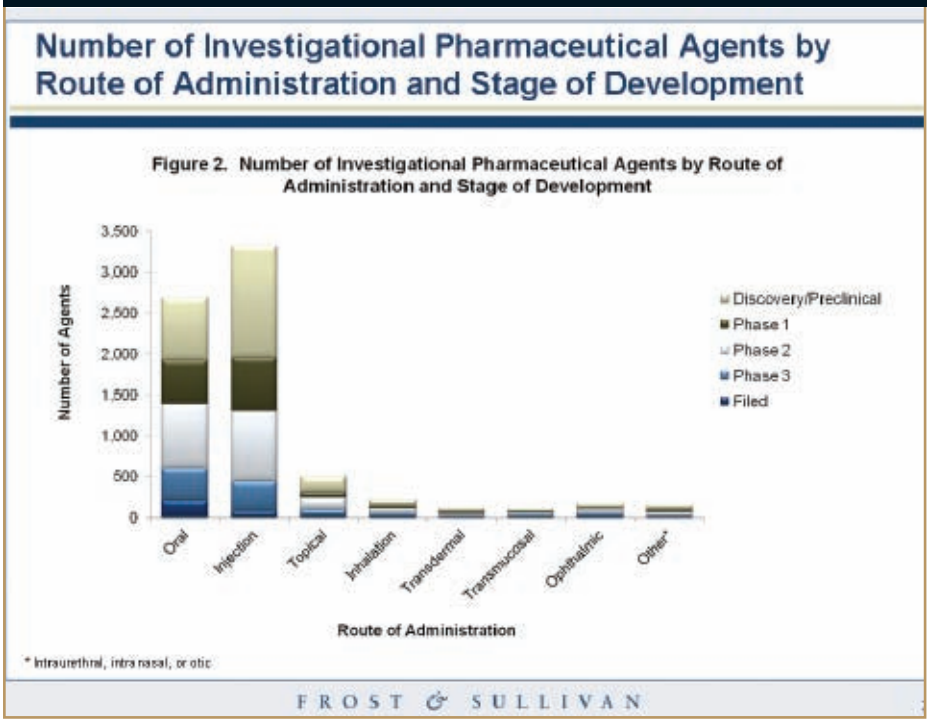
Several companies are making great strides in improving the patient experience of self-injection. For example, Ratio, Inc. has thought outside the box in developing their novel self-injection device, which resembles an adhesive patch rather than a typical pen injector. This clever device, dubbed the NuPrivo SC, is a disposable pump that slowly delivers a subcutaneous dose of medication over a period ranging from 5 seconds to 24 hours and can deliver volumes up to 5 milliliters. Rather than having to perform self-injection by pinching the skin and holding a pen injector in place, the patient simply adheres this pump-patch to a suitable location, such as the abdomen, and, with the press of a button, the device slowly injects the medication. In addition to improving ease of use, the slow delivery also reduces trauma and discomfort associated with the injection of larger volumes because the drug is allowed to slowly disperse rather than forming a pocket beneath the skin. Because the device uses hydraulic power of an expandable gel to drive the injection, the shelf-life and utility is greatly enhanced compared to a device that relies on battery power. This device could be used with any drug with no need to reformulate, and even high-viscosity formulations can be successfully delivered. The NuPrivo is slated to begin clinical trials in 2013.

FIGURE 1



Formulation improvements that extend the half-lives of drugs in the body, thus reducing the frequency of administration, are always welcomed by patients wishing to inject less often as well as physicians looking to improve their patients' compliance with their medication. There are several methods used to accomplish this, but one of the more popular is PEGylation, which involves attaching polyethylene glycol (PEG) to the drug. PEGylation is quite effective in extending the half-lives of drugs, such as peptides and antibodies, allowing for frequency of administration to be reduced from daily to weekly, or even to monthly in some cases. However, long-term exposure to PEG can result in immunogenicity reactions. In response to this issue, Caisson Biotech is capitalizing on a serendipitous discovery and is developing a non-PEG polymer based on the body's own natural, unmodified, part of the heparin sulfate molecule, heparosan. Heparosan polysaccharide sequences make up about 30% of the body's heparin sulfate (found in most cells/tissues) and heparin, but heparosan is distinctly different heparin/heparin sulfate, in that it has no heparin sulfate or heparin-like biological activity. Some pathogenic bacteria are able to synthesize heparosan and they use this to coat themselves to hide from the immune system. Because heparosan is normally present in the body, the immune system does not recognize the "heparosan-coated" bacteria as foreign. Upon discovery of the capability to synthesize this polymer at the bench, scientists at Caisson Biotech decided to put it to use to extend the half-lives of biologicals and other drugs. By attaching synthetic heparosan to a drug molecule, an extended-release formulation similar to PEGylation can be created but with much less risk of an immunogenic reaction. Additionally, the half-life of a drug-heparosan conjugate can be easily customized by simply altering the defined size of the polymer.

FIGURE 2



TARGETED DELIVERY OF RESPIRATORY VACCINES

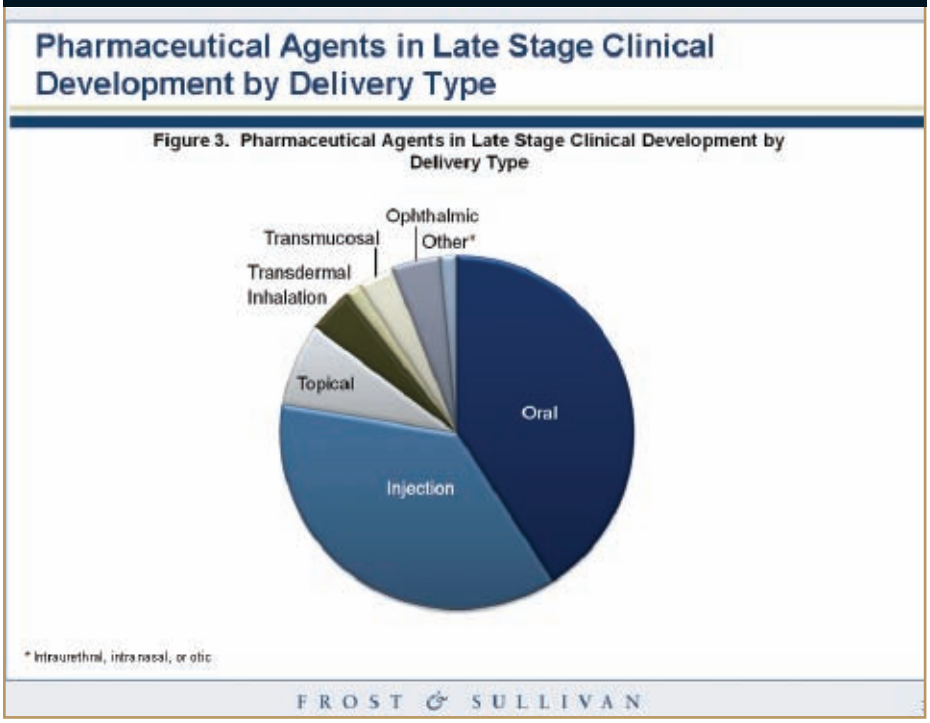
Vaccine development is one example of a highly active pharmaceuticals market segment. Vaccines have been in use since the 18th century when the vaccine for smallpox was discovered. Since then, there have been extensive improvements in the efficacy and safety of vaccines as well as the breadth of infectious diseases we can be protected against. However, vaccines are still not 100% foolproof, and there is still much room for improvement, including administration. Generally speaking, vaccines are administered via injection into the muscle, regardless of the specific pathogen being immunized against. This manner of administration typically evokes the best immune response in the patient. However, a clinical-stage Dutch biotechnology company called Mucosis is challenging this theory with its line of vaccines being developed for transmucosal administration via the nose or mouth, a method that not only is more patient friendly but has been shown to be superior in eliciting an immune response to infections such as influenza. The theory behind this novel approach is that many infectious agents, such as influenza, enter the body via the mucosal surfaces of the respiratory system, which has its own immunological defense mechanisms designed to block or inactivate pathogens. Therefore, if a vaccine is administered via the same route that the pathogen uses to invade the body, the immune response to the vaccine more closely resembles the natural immune response. Mucosis has shown that its mucosally administered vaccines can elicit both a systemic and local immune response to vaccination, which should translate into improved protection. Mucosis' lead program is SynGEM®, a mucosally administered vaccine to prevent infection by respiratory syncytial virus (RSV), a virus that commonly infects young children and the elderly for which there is currently no vaccine. SynGEM is currently in the preclinical stage of testing. Mucosis has recently announced positive results from a Phase I clinical study of FluGEM®, successfully demonstrating proof-of-concept of its vaccine technology platform dubbed Mimopath®.

TARGETED DELIVERY FOR INFLAMMATORY BOWEL DISEASE

Treatment of gastrointestinal disorders, such as inflammatory bowel disease, is one example of a therapeutic area buzzing with drug development activity due to the significant unmet need that still exists. Treatment of severe cases of inflammatory bowel disease (Crohn's disease and ulcerative colitis) has seen significant improvement with the approval of biologics, such as Remicade (infliximab, Johnson & Johnson), Humira (adalimumab, Abbott), Cimzia (certolizumab pegol, UCB), and Tysabri (natalizumab, Biogen Idec/Elan). However, systemic exposure to these and other treatments can be associated with adverse effects. Thus, pharmacotherapy of gastrointestinal disorders, such as inflammatory bowel disease, can be challenging due to the need to medicate only the bowel while avoiding unnecessary systemic exposure to the drug. If the disease is confined to the lower end of the bowel, such as in distal ulcerative colitis, localized medication can be administered via suppository, enema, or foam. However, this route of administration may not be the most preferred by the patient. Advancements in oral formulation technologies are addressing this issue by enabling the oral delivery of medications that are only released in the intestine with little to no systemic absorption, with the result of effective therapeutic treatment of the bowel and reduced side effects.

Cosmo Pharmaceuticals, based in Italy, is developing a line of products using their Multi Matrix MMX® technology that enables the controlled release of the drug in the lumen of

FIGURE 3



the colon. The technology works by using a pH-resistant coating that delays the release of the drug until it reaches the lower digestive tract, where it is slowly released, providing topical treatment at the site of inflammation, where it is needed with reduced systemic absorption. Cosmo's lead product, Lialda®, has been available in the US since 2007, where it is marketed by Shire. Lialda is a once-daily oral form of mesalamine, a drug commonly prescribed for the treatment of ulcerative colitis. A similar product with budesonide as the active ingredient is awaiting approval by the US FDA and will have the trade name of Uceris if approved. Uceris will be indicated for the treatment of ulcerative colitis as well.

Sigmoid Pharmaceuticals, located in Ireland, is developing a similar medication. Its lead product candidate for ulcerative colitis, CyCol™, has just successfully completed a Phase II clinical study. CyCol is a controlled-release formulation of cyclosporine, a powerful immunosuppressive drug. Using its proprietary drug delivery technology platform SmPill™, CyCol delivers cyclosporine directly to the colon with minimal systemic absorption, resulting in greatly improved tolerance.

Avaxia has a different approach to gastrointestinal-targeted therapy. This innovative biotech located in Massachusetts is developing oral antibodies created by collecting antibodies from the milk of immunized cows. Because antibodies secreted in the colostrum (first milk) of cows and other mammals are naturally designed to withstand degradation in the digestive tract, orally administered therapeutic antibodies can theoretically be created by immunizing cows against the desired antigen. In the case of treating inflammatory bowel disease, anti-TNF therapy is a well-established treatment for this and other autoimmune inflammatory conditions, such as rheumatoid arthritis. However, systemic administration of this drug via injection can result in unwanted side effects. By delivering anti-TNF antibodies directly to the site of inflammation in the gastrointestinal tract, Avaxia hopes to provide effective localized immunosuppressive therapy with greatly reduced side effects normally seen with the systemic delivery of TNF inhibitors, such as infections resulting from generalized immunosuppression.

CONCLUSION

A safe, effective, economical, and patient-friendly drug delivery method is a key factor for the success of a pharmaceutical product. Medicinal chemists and biologists have the critical task of discovering and developing new and innovative mechanisms that can address unmet medical needs by treating diseases more effectively and with greater safety and tolerability. Capitalizing on optimized drug delivery technologies that are designed to address both effective administration and patient acceptance can be a critical element of the final product that can take it to the next level and potentially transform a novel yet ordinary product into a potential blockbuster. ◆

BIOGRAPHY

Debbie Toscano is a Senior Industry Analyst with the Frost & Sullivan North American Healthcare practice. Utilizing more than 20 years of life sciences industry experience, she maintains particular expertise in analysis and interpretation of scientific data as well as preparation of deliverables with attention to technical detail. Mrs. Toscano has an experience base covering a broad range of sectors, including focus on diabetes and metabolic diseases, cardiovascular diseases, and preclinical animal modeling and pharmacology. Prior to joining Frost & Sullivan, she conducted preclinical research with Novartis Pharmaceuticals. Mrs. Toscano earned her BS from Delaware Valley College in Biology and her Master's Certificate from Thomas Edison State College in Clinical Trials Management.

The Future of DPIs: Aligning Design With Market Demands

By: Geralt Williams, PhD

In 1948, the first commercial dry powder inhalation device, the Aerohaler®, was launched by Abbot Laboratories. The technology seems archaic by today's standards: a deep breath in would cause a ball to strike a cartridge containing penicillin powder and shake the powder out into the airstream. However, the same device was later used to treat asthma, which set a precedent for future treatment of the disease. Today, throughout Europe, dry powder inhalers (DPIs) are used by an estimated 40% of patients to treat asthma and chronic obstructive pulmonary disease (COPD).[1]

The Aerohaler was followed by the Spinhaler® of the 1960s. The inhaler was developed for asthma treatment by Fisons Pharmaceuticals (a company later taken over by and Rhone-Poulenc Rorer, acquired by what is now known as Sanofi) and represented a breakthrough in powdered drug delivery to the lungs. By using a capsule containing the active drug, sodium cromoglycate, which was released upon inhalation, the device was very easy to use and meant that patients did not have to coordinate the inhalation of the drug with the actuation of the device.

Since this time, changes in the drug delivery market and regulatory pressures have driven innovation of DPIs forward: to-date, there are dozens of different DPI devices commercially available, and the DPI market itself is worth approximately $18 billion.[2] This article takes a look at the market forces driving DPI innovation and focuses on a novel solution that has simplicity at

FIGURE 1

Simple Steps for Operating the Twister™ DPI Device

the heart of its design, and which hopes to address the growing pressure to reduce healthcare costs, as well as the needs of new markets, arising from emerging economies in South America, India, and China.

THE ANATOMY OF A DPI

The basic components of a DPI remain the same for most types: a powder formulation, a dose mechanism containing (or measuring) a single drug dose, a powder de-agglomeration principle (which disperses the powder into the inhaled airstream), and the mouthpiece of the inhaler. Secondary parts of the inhaler have been developed to fulfill functions such as safety, ease of handling, patient feedback, and moisture protection of the drug formulation. However, throughout the past few decades, much research has focused on the design of the inhaler with respect to the most important technical aspects that ensure the right amount of drug reaches the lungs (ie, powder de-agglomeration and air flow that is generated by the patient through the inhaler and the resultant drug particle dynamics in the respiratory tract).

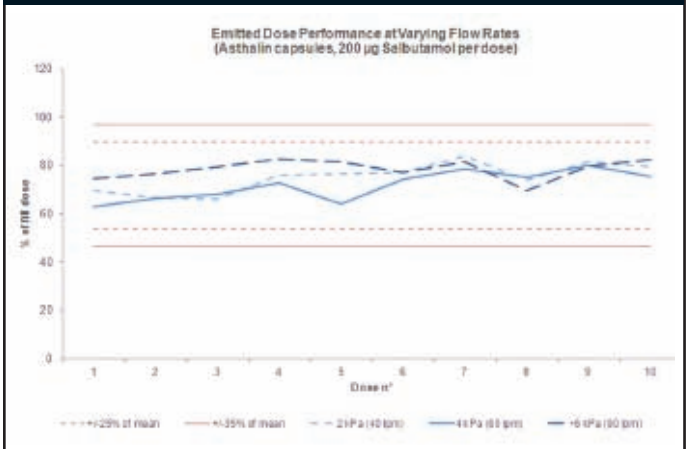
THE NEEDS OF THE DPI MARKET

The most successful DPI solutions will be those that match the changing needs of the drug delivery market as well as those of different patient groups, countries, cultures, diseases, etc as detailed below:

Reusability & Cost: Single-Dose Versus Multi-dose

As a DPI is used repeatedly by the same user, reusability is a key factor driving down the cost per dose. Single-dose inhalers, which rely on capsules to be loaded into the device, can cause difficulties for patients having to load up a capsule; there is a need, therefore, for more patient-friendly devices. Multi-dose DPIs have also been developed to overcome some of the inherent limitations of single-dose inhalers. The AB Draco company (now a division of Astra Zeneca) pioneered the design of multi-dose DPIs with their Turbuhaler®. In this device, the drug formulation is contained in a reservoir and can be dispensed into

FIGURE 2



Dose Delivery Performance at Varying Flow Rates

the dosing chamber by a twisting back and forth action at the lower end of the device. One of the criticisms of reservoir designed DPIs, however, is the delivery of the drug at variable flow rates. The issues of multiple dosing and consistent dose-to-dose delivery have been addressed with the development of individual aluminium blisters to contain the doses (as initially developed in the Diskhaler® of the 1980s by Glaxo, now GlaxoSmithKline). Multiple pre-metered dose DPIs have seen strong market growth in recent years, aided in part by the introduction of combination drugs in this category of device.

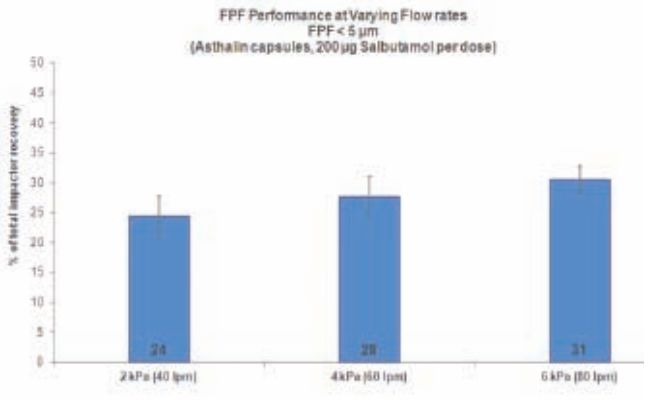
Complexity & Compliance

The way the patient uses the inhaler can play a major role in ensuring a consistent dose to the patient's lungs, therefore; capsule loading and inhalation technique are critical elements that can affect the efficacy of a DPI. It is important that patients are correctly trained to use the inhaler by the healthcare provider. Easy-to-use devices and those that can be easily taught to patients are ultimately ones that ensure high patient compliance and an accurate and acceptable dosage regime: a device requiring only a few basic steps will therefore be easy for the patient to master.

Filling Technology

The introduction of capsules has meant standardized filling technologies can be incorporated into the manufacturing process, thus meeting the needs of large-scale industrial filling of such devices, with millions of doses being manufactured yearly. Modern and accurate large-scale filling processes are also available to meet the needs of pre-metered devices (blisterstrips). With the availability of the

FIGURE 3



Fine Particle Fraction Content at Varying Flow Rates

aforementioned filling technologies, it is realistic to manufacture and fill DPIs on a large scale to meet worldwide volume needs at acceptable costs.

Regulatory Pressures

The 1987 Montreal Protocol[3], which called for the phase-out of chlorofluorocarbons (CFCs), diverted market interest away from CFC-propelled metered dose inhalers (MDIs) to DPIs; as a result, resources were channeled into creating new models of DPIs that could meet specific patient needs.[3] In the past 25 years, there have been an increasing range of regulations affecting the design, testing, and use of inhalation devices; namely for user safety, optimizing design for usability, and for re-use of individual units.[4,5] Specific guidance documents have been issued by various regulatory bodies on the subject of DPI performance and documents necessary for chemistry, manufacturing, and controls for such products.[6,7] The US market and the corresponding FDA regulatory standards in the inhalation field are probably the most challenging, eg, for issues such as moisture protection, dose content uniformity, etc, and this can lead to some products being absent from the US although present in Europe or the rest of the world.

Emerging Economies

In Asia and Latin America, asthma has been treated predominantly with pMDIs, which are considered to be a more cost-effective proposition than DPIs. However, healthcare reforms in these regions are making asthma diagnosis and medication more available to patients, so it is anticipated that the DPI growth trend will spread to these areas. The availability of low-cost, patient friendly DPI options would encourage their use in emerging economies.

EFFICACY THROUGH SIMPLICITY: TWISTER™ SETS THE RECORD STRAIGHT

Twister™ is a new cost-effective way to improve drug delivery as well as patient compliance. The design of the patient-friendly device fulfills many of the market needs described previously: the versatile and affordable, capsule-based dry powder inhaler works well with most inhaled powders on the market and is simple to use; a simple twist of the device opens the internal capsule containing the drug.

Only three simple steps are needed to operate the inhaler: Insert, Twist, and Inhale (Figure 1), and the patient is guided by various audible and visual feedbacks confirming that the full dose has been properly delivered. The capsule is easy to insert, and a healthcare provider can easily teach a patient how to use the device.

Patient safety has been optimized in the design of Twister. Unlike other DPI designs, the capsule is not pierced, which reduces the risk of contamination and the patient inhaling particles of the container closure system, improving safety. The design avoids repeated dosage as inhalation is from a single capsule only that is inserted into the device at each inhalation.

The transparent dispersion chamber makes it easy for the patient to see there is powder in the device and, after inhalation, the patient can see that they have taken the full dose providing a clear visual feedback and helping to improve compliance. The transparent chamber also allows the patient to see if cleaning is necessary.

Twister, developed by the Aptar Pharma product development team in France, has been developed for fast-growing markets but also has its place in developed markets as a low-cost alternative to pMDIs. Aptar Pharma's aim is to bring cost-effective drug delivery devices to pharmaceutical companies, helping them market affordable healthcare treatment to patients worldwide. Cost for the patient is reduced, allowing a wider range of asthma sufferers to gain better access to medication: capsules can be bought in small batches (30 or 60 capsules) by the patient to spread out the cost. The inhaler can also be used for COPD treatment, and throughout the development process, Aptar Pharma's dedicated inhalation drug formulation research team tested and collected data on various drug formulations, validating Twister as an off-the-shelf device, suitable for a variety of different drug compounds and formulations.

Twister is designed for size 3 capsules; a format suitable for high-speed filling technology, and functions with HPMC and gelatin capsule material, with a wide filling range from 5 to 30 mg. Air inlets can be tuned to adjust the device resistance, and the rotating and rattling of the capsule during inhalation helps with the de-agglomeration process.

KEY PERFORMANCE CHARACTERISTICS

Some of the performance characteristics essential to DPIs are related to dose delivery (Figure 2), fine particle fraction (FPF) content (Figure 3), and performance at varying airflows. These characteristics can vary from one powder formulation to another, and some amount of fine tuning of either device or formulation or a combination of both, may be necessary to achieve optimal performance.

PROMOTING BETTER HEALTHCARE WORLDWIDE

Dry powder inhalers have shown great promise in their ability to deliver drugs reliably and effectively, and novel designs can ensure that future cost, compliance, and safety challenges are overcome. Twister provides an easy-to-use solution that aims to meet the needs of fast-growing markets generated from emerging economies, where resources may be an issue. A key factor helping to tap into new markets are the presence of local manufacturing sites, for example, Aptar Pharma's state-of-the-art manufacturing facilities in China (Suzhou), India (Mumbai), and South America (Varela). The site in China facilitates logistical and regulatory support and allows changes in the needs of the local market to be quickly met. With the development of Twister, Aptar Pharma aims to provide a novel solution to fulfill the demands of the DPI market, whilst maintaining its goal of promoting better global healthcare access worldwide. ◆

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BIOGRAPHY

Dr. Geralt Williams is Director, Scientific Affairs, Aptar Pharma, Prescription Division, France. After earning his PhD from the University of Wales, UK in 1985, he has held various industrial positions at Monsanto Inc. (UK), Fisons Ltd (UK), Valois (France), and Inhale/Nektar Therapeutics (USA). He is now in charge of scientific affairs for the Aptar Pharma Prescription division, Le Vaudreuil, France, and is engaged in the development of new devices for nasal and inhaled drug products.

KinetiSol®: A New Processing Paradigm for Amorphous Solid Dispersion Systems

By: Dave A. Miller, PhD; James C. DiNunzio, PhD; Justin R. Hughey, PhD; Robert O. Williams III, PhD; and James W. McGinity, PhD

ABSTRACT

The number of poorly water-soluble compounds in development pipelines continues to increase, and the properties of these molecules are deviating further and further from conventional drug-like characteristics. Amorphous solid dispersions are becoming widely utilized to manage solubility issues as evidenced by the increasing number of marketed drug products based on this formulation technology. Hot-melt extrusion (HME) and spray drying are the leading processing technologies for amorphous dispersion systems; however, recent trends in molecular properties have led to a subset of insoluble molecules that are difficult or impossible to process by these methods. KinetiSol, a novel fusion-based process for the production of amorphous solid dispersion systems, has recently been adapted to pharmaceutical processing, and with its unique process attributes, is providing novel solutions for difficult-to-process compounds. KinetiSol's brief processing times, low processing temperatures, high mixing intensity, and lack of torque limitations offer unprecedented capabilities for amorphous dispersion production with thermally sensitive active pharmaceutical ingredients (APIs) and excipients, high melting point APIs, and highly viscous polymers. Moreover, KinetiSol offers the operational, environmental, and economic benefits of non-solvent processing. The attributes of the KinetiSol process, its novel applications to the field of amorphous solid dispersion processing, and its value as a commercial pharmaceutical manufacturing process are presented herein with a review of the current literature on the technology.

INTRODUCTION

Since the advent of high throughput screening methodologies in drug discovery, the percentage of poorly water-soluble (PWS) drug candidates in development has continuously increased.[1] Molecules emerging from discovery groups of late are continuing to deviate further from conventional drug-like properties as the boundaries of chemical space are constantly expanded in search of new and better drugs. Based on the pharmaceutical literature and the authors' experience, the percentage of PWS drug candidates in contemporary drug development pipelines can range from 40% to 90%, depending on therapeutic area.[2,3]

Amorphous solid dispersion (ASD) systems have recently emerged as a leading strategy for managing the solubility-related challenges of today's new chemical entities (NCEs). Early reviews on

FIGURE 1

Lab-scale GMP KinetiSol Compounder.

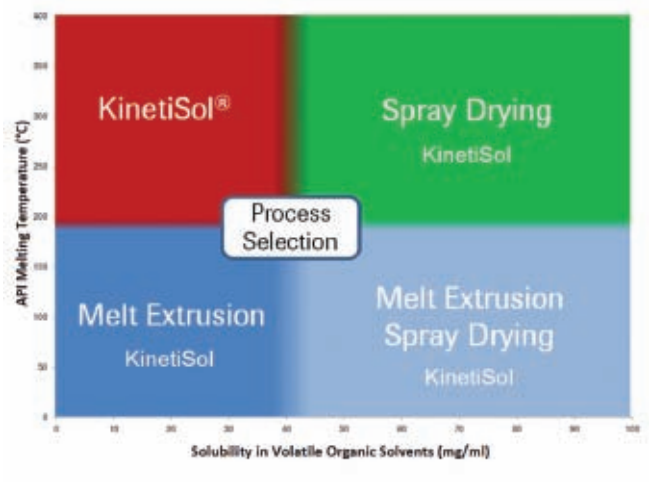
ASD systems pointed toward the lack of commercial products as an indicator of limited commercial viability of amorphous technologies and/or concerns with regard to the risk of physical instability. However, since this time, several products based on ASD technologies have been commercialized, including: Kaletra®, Norvir®, Prograf®, Spranox®, Zelboraf®, Intelence®, Incivek®, and Kalydeco®. The increasing number of ASD products on the market indicates industry acceptance and demonstrates the commercial viability of amorphous formulation technologies.

There are two primary approaches for producing ASD compositions: (1) fusion-based and (2) solvent-based methods.[4] Although numerous technologies have been developed as derivatives of these two fundamental approaches, HME and spray drying are recognized as the leading technologies. Both processes were established commercial technologies in other industries prior to their adaptation to pharmaceutical manufacturing and are now widely applied in the pharmaceutical industry.[5,6]

A new technology to the field of solid dispersion processing, KinetiSol, has recently emerged in the pharmaceutical literature and has been demonstrated to produce ASD systems with the most challenging compounds and compositions. Like HME and spray drying, the basis of KinetiSol was established in another industry, commercial plastics processing, prior to its adaptation for pharmaceutical manufacturing. The viability of the KinetiSol process for production of pharmaceutical ASD systems was first established at a commercial scale and then subsequently scaled down to accommodate pharmaceutical laboratory environments and to minimize API consumption during formulations development.[7] A lab-scale KinetiSol compounder, suitable for GMP use, is pictured in Figure 1.

KinetiSol is a fusion-based process that utilizes frictional and shear energies to rapidly transition drug-polymer blends into a molten state. Simultaneous to the molten transition, KinetiSol rapidly and thoroughly mixes the active ingredient with its excipient carrier(s) on a molecular level to achieve a single-phase ASD system. The real-time temperature of the composition within the KinetiSol chamber is monitored by a computer-control module, and upon reaching the user defined endpoint, molten material is immediately ejected from the process. Total processing times are generally less than 20 seconds, and elevated temperatures are observed for typically less than 5 seconds before discharge and cooling. On a lab-scale, the process is designed to operate in batch mode, whereas in commercial processing, it is operated semi-continuously, achieving product throughput as high as 1,000 kg/hr.

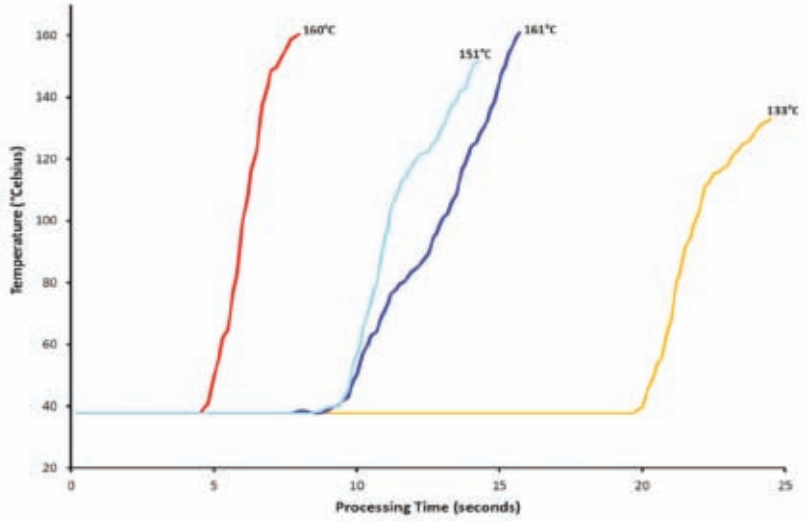
FIGURE 2



Schematic illustrating process selection rationale as a function of API melting point and solubility in volatile organic solvents.

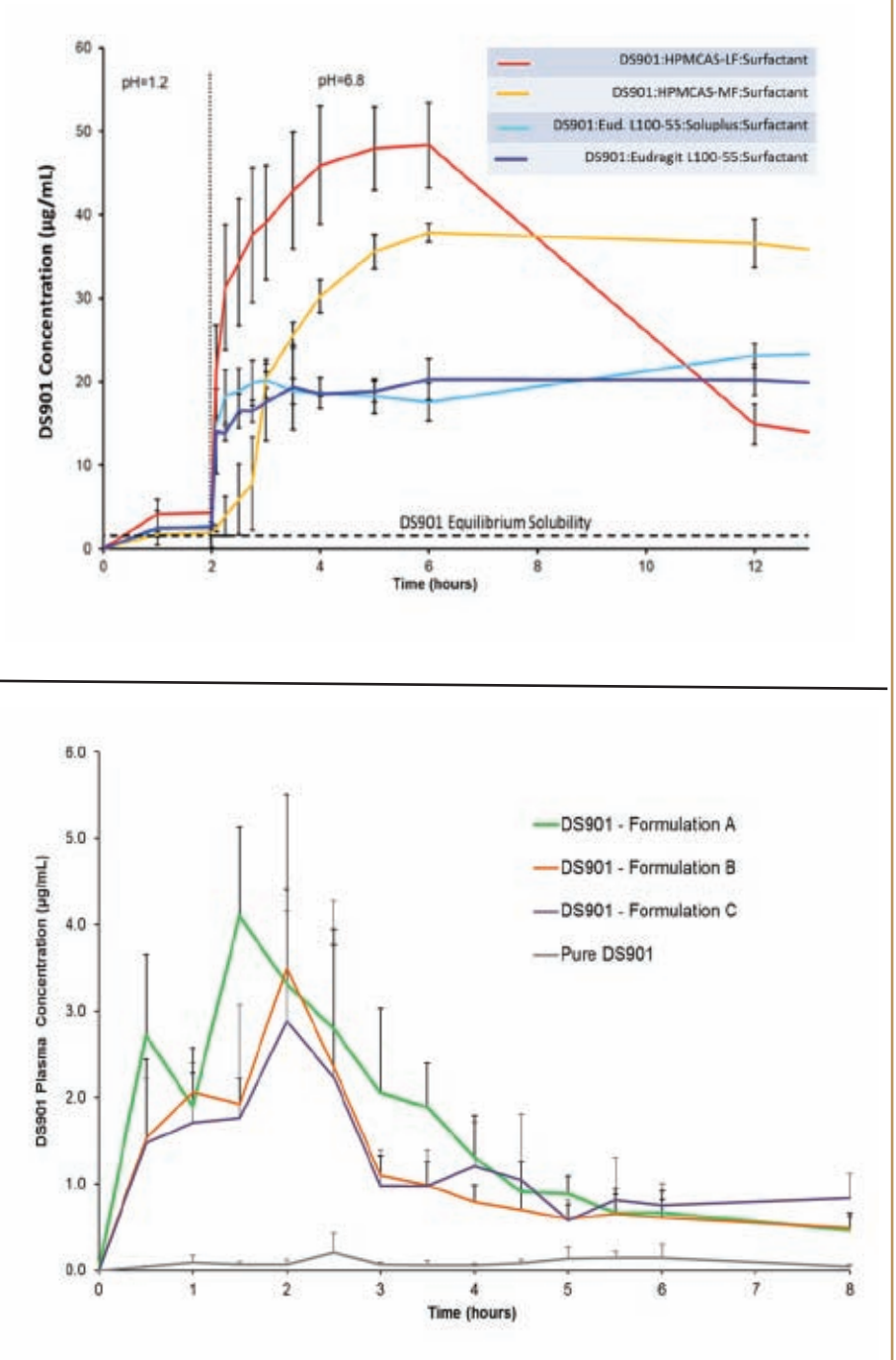
With its unique attributes, the KinetiSol process is providing novel solutions to emerging problems associated with ASD processing. KinetiSol's very brief processing times enable production of ASD systems with thermally sensitive APIs and excipients. The high rates of shear inherent to KinetiSol accelerate solubilization kinetics of drug compounds in molten polymers, which typically results in processing temperatures that are well below the melting point of the API. Consequently, the production of ASD systems with high melting point compounds (>200°C)

FIGURE 3



KinetiSol processing profiles for DS901 with four polymeric carriers.

FIGURE 4A&B



(A) Non-sink, gastric transfer dissolution testing of four DS901 KinetiSol compositions. (B) DS901 plasma concentration profiles from oral dosing of three KinetiSol compositions and pure crystalline drug in male Sprague-Dawley rats (50 mg/kg).

in a broad spectrum of concentration-enhancing polymers is routinely achieved with KinetiSol. The KinetiSol process is not torque limited, and hence processing of highly viscous/non-thermoplastic/high molecular weight polymers can be easily accomplished without the use of plasticizers. The capabilities of KinetiSol enable the use of unique drug/excipient combinations to create solubility-enhanced compositions that cannot be reproduced or manufactured at large scales by other technologies.

As established technologies in pharmaceutical manufacturing, HME and spray drying are the primary options for most PWS compounds. For molecules with acceptable thermal properties, HME is typically the technology of choice. When thermal properties are an issue, yet solubility in a volatile organic solvent is acceptable, spray drying is often the selected approach. Challenges for technology selection exist when compounds possess unacceptable thermal properties for HME and poor solubility in suitable organic solvents. It is in this area where KinetiSol provides considerable value. As a non-solvent process that can rapidly solubilize high melting point APIs in molten polymers, KinetiSol is able to satisfy unmet needs in this area of the PWS compound space. KinetiSol also supplements HME and spray drying in other areas when molecules are thermally labile or unstable in organic solution, for example. Additionally, KinetiSol may be an alternative to spray drying when cost of goods or the availability of high volume manufacturing capacity is an issue. The schematic shown in Figure 2 illustrates the rationale for process selection between HME, spray drying, and KinetiSol based on API melting point and solubility in volatile organic solvents. KinetiSol shown in a smaller font represents instances when the primary technology cannot be utilized for reasons such as those mentioned earlier.

With the increasing challenges of PWS drugs, unmet needs are emerging that cannot be satisfied with only HME and spray drying. KinetiSol offers unique and viable solutions to these issues and consequently adds substantial value to the field of ASD technologies. This article presents the unique attributes of the KinetiSol process and its novel applications to the production of ASD systems by reviewing the current literature on the technology.

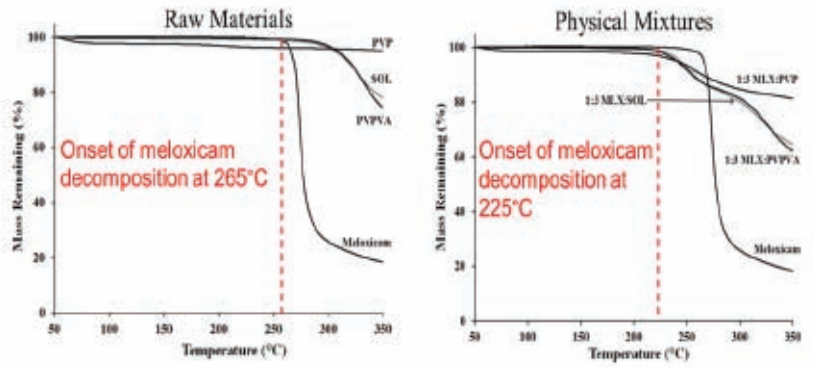
KINETISOL PROCESSING OF HIGH MELTING POINT DRUGS

PWS drugs with very high melting points (>200°C) are emerging from drug discovery

with greater frequency in recent years. High melting point compounds present significant challenges to thermal processing for the production of ASD systems, namely carrier degradation and amorphous drug-loading limitations. When processing these compounds by HME, extrusion temperatures are limited by the onset of thermal degradation of the polymer carrier, and thus processing temperatures can be 100°C or more below the melting point of the drug. In this processing regime, the drug must be solubilized by the molten polymer in order to achieve an amorphous composition. Solubilization of the API in the molten polymer is controlled by dissolution kinetics, and typically, the time required to solubilize the drug fraction is proportional to its melting point. This requires the use of a carrier that is capable of fully and rapidly solubilizing the API at temperatures well below its melting point, which limits the range of excipients available for formulation design. For very high melting point compounds, it can be extremely difficult or impossible to achieve target drug loads without extended residence time distributions, greater mechanical energy input, and/or high temperatures, all of which can lead to degradation of the API and/or polymer carrier.

The advantage of KinetiSol for thermal processing of high melting point compounds is two-fold: (1) the energy input typically renders crystalline compounds amorphous well below their melting points and (2) the process's high shear rates significantly accelerate solubilization kinetics of APIs in molten polymers. Consequently, KinetiSol can render high melting point APIs amorphous at temperatures well within the thermal limits of most pharmaceutical polymers. Additionally, the rapid solubilization kinetics provided by KinetiSol allow for the achievement of high amorphous drug loadings. In this section, case studies are reviewed, illustrating the applicability of KinetiSol to the production of ASD systems with high melting point compounds.

FIGURE 5



TGA analysis of meloxicam, Povidone (PVP), Soluplus (Sol), copovidone (PVPVA), and 1:3 physical mixtures of meloxicam with each polymer. Reprinted with permission from Reference 8.

DS901

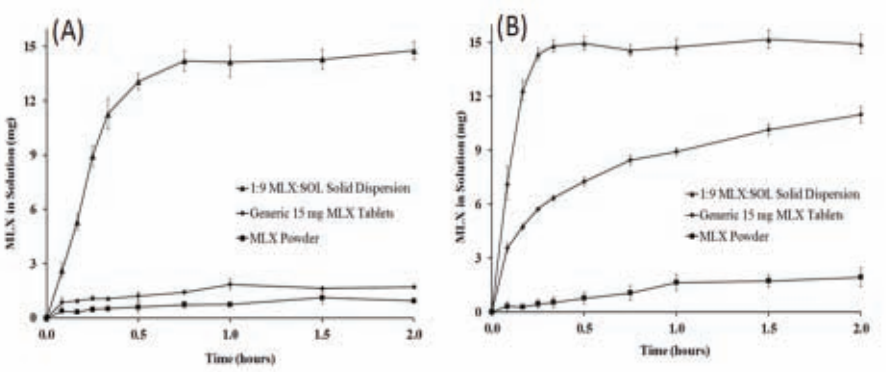
DS901 is an experimental oncology compound that has demonstrated compelling efficacy in aggressive cancer models. The solubility of the compound in aqueous media is less than 2 µg/mL across the physiologically relevant pH range. The melting point of DS901 is 295°C as determined by DSC, and efforts to solubilize this molecule at target amorphous drug loadings using HME were unsuccessful. Although the compound exhibits a high LogP value (8.1), its apparent caco-2 permeability (Pap_p) was determined to be less than 1 x 10^{-6} cm/s, suggesting that DS901 is a BCS IV compound.

KinetiSol processing was successfully applied to produce ASD compositions of DS901 with four different polymeric carrier systems: HPMCAS-LF, HPMCAS-MF, Eudragit® L100-55, and Soluplus® in combination with Eudragit® L100-55; each also containing a surfactant. The KinetiSol process temperature profiles for each composition are shown in Figure 3. It can be seen that all compositions were rendered amorphous at peak temperatures as much as 160°C below the melting point of the drug. Also, processing times at elevated temperature were less than 5 seconds for all compositions, demonstrating the rapid solubilization kinetics achieved with KinetiSol. Potency analysis revealed that the DS901 content in all formulations was in excess of 99%.

Non-sink, gastric transfer dissolution testing revealed vast improvements in the dissolution properties of DS901 for all KinetiSol compositions over the pure compound; however, the HPMCAS-LF-based formulation was determined to be superior with respect to extent of DS901 supersaturation (Figure 4A). Pharmacokinetic studies in male Sprague-Dawley rats were conducted to compare the oral absorption of DS901 from the best KinetiSol compositions versus the micronized crystalline drug. As seen in Figure 4B, all KinetiSol compositions generated substantial improvements in systemic concentrations of DS901 over the pure drug.

The results of KinetiSol processing with DS901 illustrate the capability of the process to achieve target amorphous drug loadings of very high melting point compounds in various solubility-enhancing polymeric carriers. The resulting KinetiSol formulations generated substantial supersaturation of DS901 in simulated intestinal fluids and significantly enhanced the oral bioavailability of DS901. These results demonstrated the enablement of a potential new cancer therapy by the application of the KinetiSol technology.

FIGURE 6



Non-sink dissolution analysis of the KinetiSol composition versus a commercial MLX tablet and pure MLX in: (A) 0.1N HCl and (B) water at 37°C. Reprinted with permission from Reference 8.

Meloxicam

Meloxicam (MLX) is another example of a very high melting point compound with poor aqueous solubility that presents significant challenges for thermal processing. MLX is a non-steroidal, anti-inflammatory drug. Upon melting at 270°C, MLX rapidly decomposes. The compound is classified as a BCS II with solubility values in hydrochloric acid and purified water of 0.9 µg/mL and 12 µg/mL, respectively.

In a recent study, Hughey and co-workers evaluated thermal processing of MLX to achieve solubility enhanced formulation systems.[8] The goals of these experiments were to identify polymeric carriers that enabled production of chemically stable, single-phase ASDs of MLX. Polymer screening studies demonstrated that MLX was more soluble in the Soluplus than povidone and copovidone. TGA with the physical blends (1:3, MLX:polymeric carrier) demonstrated that MLX decomposition occurred at approximately 40°C below its melting point without mixing, indicating that fusion processing would be problematic (Figure 5). The preparation of amorphous dispersion systems of MLX in Soluplus by HME required processing temperatures of 175ºC and yielded only 88% potency. With KinetiSol, processing temperatures were limited to 110ºC, and residence times were reduced to seconds, effectively limiting impurity formation and yielding a product potency of 98%.

The dissolution performance of the amorphous MLX:Soluplus KinetiSol composition was evaluated against a commercial MLX tablet and pure MLX by non-sink dissolution testing in 0.1 N HCl and deionized water. As seen from the dissolution profiles in Figure 6, a significant increase of dissolution rate was achieved with the KinetiSol solid dispersion versus the MLX tablet and pure MLX in both 0.1 N HCl and deionized water. These results thus demonstrated the potential of KinetiSol to enhance both the rate and extent of dissolution with a high melting point, thermally unstable, PWS compound.

KINETISOL PROCESSING OF THERMALLY LABILE DRUGS

Many PWS compounds in today's development pipelines exhibit thermal degradation characteristics in addition to other properties that limit thermal processing, ie, high melting points. Thermal degradation of a material is most typically the result of cumulative heat exposure, which is a function of temperature and time. Therefore, the use of HME for the production of ASDs can be limited for thermally labile compounds owing to tailing residence time distributions that can expose processed materials to elevated temperatures for several minutes.

Conversely, KinetiSol processing limits exposure to elevated temperatures to just a few seconds. Moreover, peak process temperatures are often reduced compared to HME because high shear mixing allows for improved compound solubilization at lower temperatures. Therefore, KinetiSol offers significant advantages to the processing of thermally labile compounds as it reduces cumulative heat exposure through shorter processing times and lower processing temperatures.

ROA

One such example of an insoluble NCE exhibiting thermal instability is ROA, which is both acid and heat labile and decomposes at its melting point of 230°C.[9] The compound is BCS II and has a solubility in simulated gastric fluid of 3 µg/mL and a solubility in FaSSIF of 7 µg/mL. Eudragit L100-55 and HPMCAS-LF were the two polymers selected to prepare molecular dispersions of ROA by KinetiSol. TGA studies revealed that ROA degraded at a faster rate at elevated temperatures when in the presence of the enteric polymers (Figure 7). This is presumably due to the instability of ROA in acidic environments and the abundance of acidic functional groups on the Eudragit L100-55 and HPMCAS-LF polymers. Faster rates of degradation in the presence of Eudragit L100-55 were also ascribed to the greater concentration of free carboxyl groups and lower pH in aqueous dispersion versus HPMCAS-LF. The acceleration of thermal degradation in the presence of the anionic polymers presented even greater challenges to the thermal processing of ROA.

The KinetiSol processing times at elevated temperature for the ROA-Eudragit L100-55 and ROA-HPMCAS-LF were limited to a few seconds and both ejection temperatures were less than 120°C, demonstrating processing temperatures far

below the ROA melting point. When processed by HME, residence times were on the order of minutes and processing temperatures of 140°C and 170°C were required to render ROA substantially amorphous in the Eudragit L100-55 and HPMCAS-LF compositions, respectively.

Potency analysis of the amorphous dispersion systems revealed that drug recovery was substantially higher with KinetiSol versus HME for comparable process feeds. In the case of Eudragit L100-55, the mean ROA recovery value was 70.9% for KinetiSol and 22.7% for HME. The mean drug recovery value for the HPMCAS-LF composition was 99.4% with KinetiSol and 70.9% for HME. A comparative summary of processing parameters and chemical analysis of the KinetiSol and HME products is provided in Table 1.

Non-sink dissolution testing of all compositions demonstrated rapid supersaturation after acid-to-neutral pH adjustment to approximately two to three times the equilibrium solubility of ROA, which was maintained for at least 24 hours. The results of the study demonstrated that KinetiSol was an effective method of producing solubility-enhanced ASD compositions where HME was not feasible owing to the compound's high melting point and thermal instability.

Hydrocortisone

DiNunzio et al investigated thermal processing of hydrocortisone (HCT), a heat-labile steroid, with two polymer carriers, HPMC E3 and PVPVA 64, by HME and KinetiSol.[10] HME manufacturing of the HCT-HPMC E3 composition could not be conducted at process temperatures below 180°C, and compositions produced at 180°C were determined to be only 75% of theoretical potency. The major impurity peak resulting from processing was determined to be the result of oxidative decomposition.

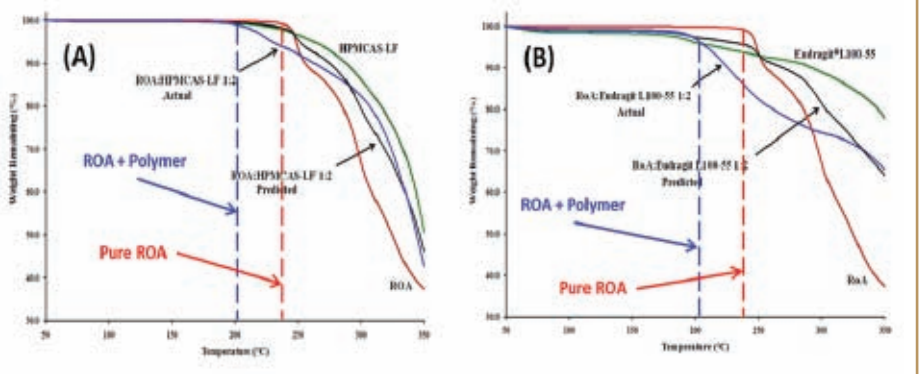
When processed by KinetiSol at 180°C, the HCT-HPMC E3 solid dispersion was found to yield an assay value of 83%. A further potency improvement could be obtained with KinetiSol, where HCT-HPMC E3 compositions were able to be processed to a 160°C endpoint to achieve an amorphous dispersion at 91.9% of target potency. Due to its unique characteristics, KinetiSol enabled processing at lower temperatures and for shorter durations, which reduced degradation of HCT.

For the HCT-PVPVA 64 composition, HME processing was possible at 160°C, owing to the reduced viscosity of the polymer. The extrudate product at this processing temperature was determined to be 97.4% of the theoretical drug content. Similarly, the HCT-PVPVA 64 composition when processed by KinetiSol at an ejection temperature of 160°C was found to yield an assay value of 98.3%. Improved product potency with the PVPVA 64 carrier over the HPMC E3 carrier was attributed to improved chemical compatibility with HCT. The abundance of hydroxyl groups on the HPMC carrier was theorized to have contributed to oxidation of the compound. Subsequent HME trials with the PVPVA 64 carrier at elevated temperatures and extended residence time revealed that product potency was inversely related to process temperature and time. This evaluation of thermal processing of HCT compositions revealed that thermal exposure was minimized via lower temperatures and reduced residence times, and thus KinetiSol provided improved product potencies versus HME.

KINETISOL PROCESSING OF THERMALLY SENSITIVE, HIGHLY VISCOUS POLYMER SYSTEMS WITHOUT PLASTICIZERS

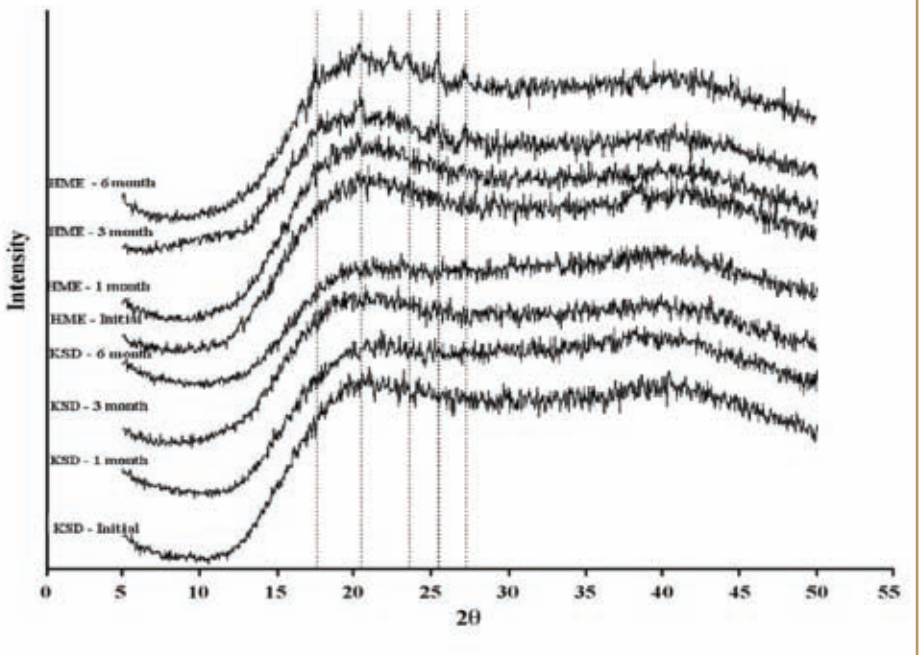
Many of the polymers commonly used in solid dispersion systems present challenges for fusion-based processing with respect to thermal sensitivity, high viscosity, or both. Often, plasticizers and other processing aids are required to reduce polymer glass transition temperatures to enable thermal processing of viscous systems or to facilitate thermal processing at lower temperatures. Because KinetiSol is not torque-limited, highly viscous polymer systems are no issue to process without plasticizers. Furthermore, KinetiSol's very brief processing times at elevated temperature (typically less than 5 seconds) reduce thermal stress on the polymer, and hence reduction of process temperatures by incorporating a plasticizer is not required. Even further, the unique modes of shear induced by KinetiSol facilitate amorphous composition formation well below the melting point of most drugs, thus processing temperatures are typically lower with KinetiSol than HME. The elimination of plasticizers leads to increased

FIGURE 7



Thermogravimetric analysis of: (A) ROA with HPMCAS-LF and (B) ROA with Eudragit L100-55. Reprinted with permission from Reference 9.

FIGURE 8



XRD patterns of HME and KSD process ITZ:L100 solid dispersions measured over 6 months accelerated stability at 40°C/75% RH. Reprinted with permission from Reference 11.

composite glass transition temperatures and improved physical stability, in most cases.

DiNunzio et al evaluated this aspect of KinetiSol versus HME in the production of ASD systems with ITZ and Eudragit L100-55 as a lone carrier and in conjunction with Carbopol 974P.[11] Eudragit L100-55 is an anionic polymer with an onset of dissolution at pH 5.5 that has been shown to provide extensive enhancement of oral absorption of PWS drugs by targeting supersaturation to the proximal small intestine.[12] However, Eudragit L100-55 is a heat labile polymer, which undergoes thermal degradation at approximately 155°C by decomposition of carboxylic acid side chains followed by chain decomposition above 180°C.[13] Its thermal sensitivity coupled with high molten viscosity make Eudragit L100-55 a particularly challenging polymer to process thermally, and hence plasticizers are almost always required when processing by HME. This was the case in the study by DiNunzio et al where Eudragit L100-55-based compositions prepared by HME required the aid of a plasticizer to achieve the necessary viscoelastic characteristics to enable processing. However, enablement of processing was achieved to the detriment of molecular immobility as these materials exhibited a reduced compositional glass transition temperature of 54°C.

Conversely, KinetiSol processing allowed for the production of ASDs without the aid of a plasticizer, resulting in an amorphous ITZ-Eudragit L100-55 (1:2) composition with a measured glass transition temperature of 101°C. Examination of side group functionality of KinetiSol processed L100-55 compositions showed similar functional levels to that of the unprocessed polymer, indicating that the polymer was not degraded during processing despite being processed above its degradation onset temperature. This result is attributed to KinetiSol's brief processing times that limit exposure to elevated temperatures to just a few seconds.

This difference in composite glass transition temperatures between plasticized HME compositions and non-plasticized KinetiSol compositions was found to directly correlate with physical stability as shown in Figure 8. ITZ crystallization was identified with the plasticized HME composition after just 1 month storage at 40°C/75% RH; whereas, the non-plasticized KinetiSol composition remained stable for the entire 6-month study duration.

In this study, DiNunzio et al also investigated the incorporation of Carbopol 974P into the ITZ-Eudragit L100-55 system. These researchers determined that KinetiSol was able to produce a single-phase system with ITZ, Eudragit L100-55, and the cross-linked Carbopol 974P without the use of a plasticizer. This same composition when processed by HME required a plasticizer and was determined to be two-phase with respect to the polymer carriers. This example illustrates the unique capability of KinetiSol to make compatible liner and cross-linked polymer systems to form a single-phase polymeric composite. This ability of KinetiSol to process highly viscous, cross-linked polymers is an attribute that allows it to stand out in the field of plastics processing. The ability to combine linear and cross-linked polymers creates new possibilities for the incorporation of cross-linked excipients, eg, carbomer and crospovidone, into solid dispersion systems.

Although DiNunzio et al demonstrated enhanced dissolution performance with the presence of TEC in both the HME and KinetiSol compositions, this was attributed to pore formation caused by leaching of the water-miscible plasticizer in the acidic phase of the dissolution test. Such pore formation could be achieved with a number of water-soluble excipients; eg, surfactants, low MW polymers; and is not specific to TEC. Moreover, non-plasticizing excipients would not negatively impact the composite glass transition temperature and consequently the physical stability of the amorphous dispersion.

This study thus established the unique ability of KinetiSol to process thermally

sensitive, highly viscous polymers without use of a plasticizer and the corresponding improvement in physical stability of the resulting amorphous dispersion. It also demonstrated the ability of KinetiSol to homogenously process a highly viscous, cross-linked polymer into an amorphous dispersion without use of a plasticizer and perhaps presented new possibilities for the use of cross-linked materials for solubility-enhancement applications.

KINETISOL PROCESSING WITH A NON-THERMOPLASTIC POLYMER FOR IMPROVED HOMOGENEITY

Cellulosic polymers, such as HPMC and HPMCAS, have proven to be amongst the most effective concentration-enhancing polymers, yielding extensive and prolonged supersaturation from various ASD systems.[14-16] However, specific cellulosic derivatives, such as HPMCs, are non-thermoplastic polymers and as such are difficult to process thermally; often leading to heterogeneous, multi-phase systems.[17,18] Such an issue was reported by Six et al with the use of HME to produce ASDs of itraconazole with HPMC.[17,18] Although the composition produced significant improvement in dissolution properties and oral bioavailability of ITZ, it was determined to be non-homogeneous.[17] DSC analysis of the HME-processed formulation revealed two distinct glass transition temperatures, indicating drug rich and polymer rich domains.

In a study conducted by DiNunzio et al, thermal processing of ITZ and HPMC by both HME and KinetiSol was investigated.[19] Similar to the findings of Six et al, DiNunzio and co-workers determined that ITZ:HPMC E5 (1:2) ASD systems produced by HME were two-phase. Conversely, these authors determined that the same composition processed by KinetiSol yielded a single-phase amorphous dispersion as indicated by a single glass transition temperature at 86.02°C. A comparison of the thermograms for the HME and KinetiSol processed systems is shown in Figure 9.

TABLE 1

KinetiSol Compositions

Polymer	Particle Size	Speed (RPM)	Temp. (°C)	Potency (%)	Impurities (%)
Eudragit® L100-55	Unmicronized	1,450	100	70.9 ± 0.8	12.9
HPMCAS	Unmicronized	2400	112	99.4 ± 1.2	1.6

Hot-Melt Extrusion Compositions

Polymer	Particle Size	Processing Temp. (°C)	Screw Speed (rpm)	Recirculation Time (min)	Potency (%)	Impurities (%)
Eudragit® L100-55	Unmicronized	140	300	2	22.7 ± 0.5	55.9
HPMCAS	Unmicronized	170	300	2	70.9 ± 0.3	10.2

Summary of processing parameters and chemical analysis of ROA compositions with Eudragit L100-55 and HPMCAS-LF produced with KinetiSol and HME. Adapted from Reference 9.

The authors attributed the improved homogeneity of the KinetiSol-processed system to the higher shear rates, which provided enhanced mixing characteristics with respect to HME. This improved mixing was purported to facilitate micro and nano-scale mixing, resulting in a more homogenous solid dispersion. Also, rapid processing in the molten state followed by rapid quenching may have prevented phase separation of the two components in situ.

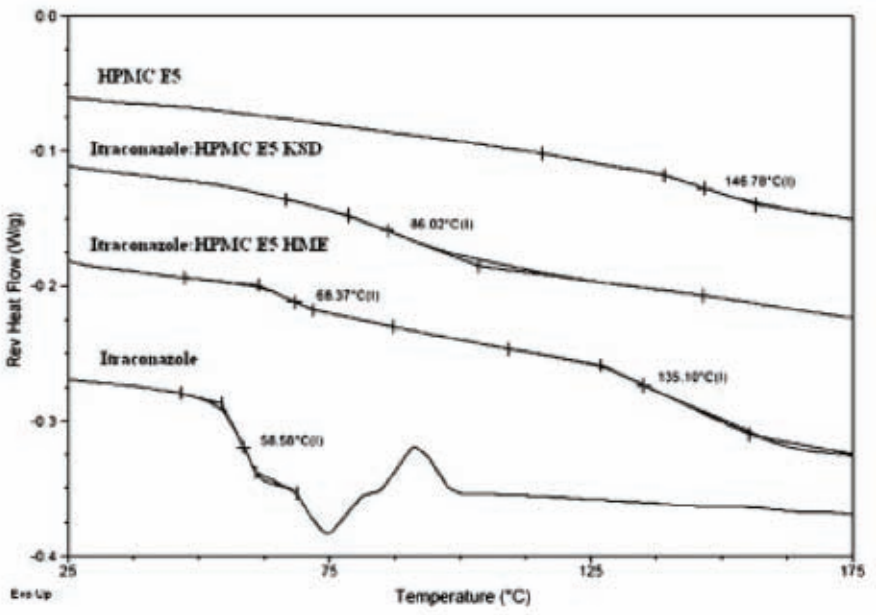
The more homogenous, single-phase KinetiSol-processed ITZ:HPMC E5 system was also determined to produce superior performance characteristics exhibiting more rapid and extensive supersaturation of ITZ in simulated gastric media versus the HME system. The dissolution result correlated with the results of mDSC in that the dissolution rate of the more homogenous KinetiSol system would be governed primarily by the hydrophilic polymer, while the heterogeneous HME system containing drug rich, hydrophobic domains would dissolve more slowly. The authors stated that the faster dissolution rate of the KinetiSol system highlighted the advantage of enhanced mixing with KinetiSol processing, which may lead to compositions with improved therapeutic performance. However, for this system, the enhanced dissolution rate did not yield a statistically significant improvement in oral absorption in rats versus HME.

This study illustrates that according to its high mixing intensity and rapid processing times, KinetiSol can effectively thermally mix APIs with non-thermoplastic polymers to achieve homogenous, single-phase amorphous dispersions. Improved homogeneity was determined to enhance dissolution performance in this study. This advantage presumably would also enhance physical stability by generating more intimate interactions between the drug and polymer as well as allowing the polymer to function more effectively as a steric barrier to nucleation and recrystallization of drug molecules.

CONCLUSION

In this article, the unique capabilities of the KinetiSol process and its novel applications to the production of ASD systems have been reviewed. KinetiSol was demonstrated to

FIGURE 9



Reversing heat flow profiles of amorphous ITZ, HPMC E5, and ITZ:HPMC E5 solid dispersions produced by HME and KinetiSol. Reprinted with permission from Reference 19.

enable thermal processing of heat-labile APIs by reducing processing temperatures and durations. The rapid solubilization kinetics inherent to the KinetiSol process were shown to enable the achievement of ASD systems with very high melting point compounds in various polymeric carriers. KinetiSol was shown to enable processing of highly viscous, thermally unstable polymers without the use of plasticizers. Finally, the high intensity mixing inherent to KinetiSol was also demonstrated to produce single-phase ASDs with non-thermoplastic, concentration-enhancing polymers.

According to its unique attributes and novel applications to the production of ASD systems, KinetiSol is providing solutions to unmet needs for the pharmaceutical industry's most challenging PWS molecules. As small molecules in discovery pipelines continue to diverge from traditional drug-like properties, these problems will become increasingly more prevalent. Consequently, novel platform technologies such as KinetiSol will be needed to enable the development of new medicinal therapies from promising drug candidates. ◆

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BIOGRAPHIES

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Dr. Justin R. Hughey serves as the Director of Research for Enavail, LLC. He earned a BS in Chemical Engineering from The University of Texas at Austin, a BS in Chemistry from Texas State University, and his PhD in Pharmaceutics from The University of Texas at Austin. While earning his PhD, he interned in the Solid Oral Dosage Form group at Bend Research Inc. in Bend, OR. His research interests are focused on novel formulation and processing techniques to enhance the solubility of thermally labile and high melting point drug substances exhibiting poor aqueous solubility; applications of hot-melt extrusion technology for immediate release, controlled release, and solubility enhancement applications; particle engineering technologies for oral, pulmonary, nasal, and buccal delivery, controlled, and immediate release tablets; as well as analytical method development. Dr. Hughey has published and presented over 20 articles and abstracts, authored three book chapters and is co-inventor on seven patent applications.

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Improvements in Characterization of Pharmaceuticals: Fast Scanning Rate DSC Methods

By: Kevin P. Menard, PhD, MBA

ABSTRACT

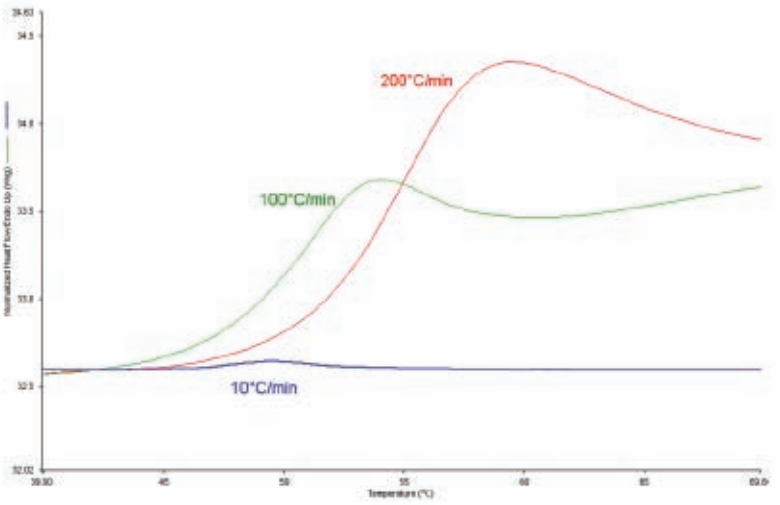
Fast scanning rate Differential Scanning Calorimetry (DSC) represents a recent and underutilized technique for the characterization of pharmaceutical materials. Applications range from measuring melting points and purity to detection of low levels of amorphous material and polymorphic forms. Several of the more common applications are discussed.

INTRODUCTION

Physical characterization of pharmaceuticals remains an important tool for the pharmaceutical chemist in R&D, formulation, and QA/QC. Information about the purity of a material, its polymorphic composition, the presence of excipients, the amount of amorphous material present, and the glass transition of lyophilized materials are all obtained via thermal methods like Differential Scanning Calorimetry (DSC). Because of this, a DSC is a familiar tool in most pharmaceutical laboratories. However, many users are still aware of the increases in sensitivity and other advantages of Fast Scanning Rate DSC techniques.

Fast Scanning Rate DSC, better known under its trade name from PerkinElmer® as HyperDSC™, is a technique in which the sample is heated or cooled at rates of 200°C or greater per minute over the same temperature range as is used in Conventional DSC. Fast Scanning Rate DSC exploits the standard heat flow equations to increase the sensitivity of the instrument by using increased heating rates (Figure 1). Because of the design of power compensation, DSC, with its very small

FIGURE 1



The glass transition (Tg) of nifedipine is shown at three heating rates, demonstrating the increase in sensitivity caused by HyperDSC. The same sample was used for all three, and no calibrations were changed between runs.

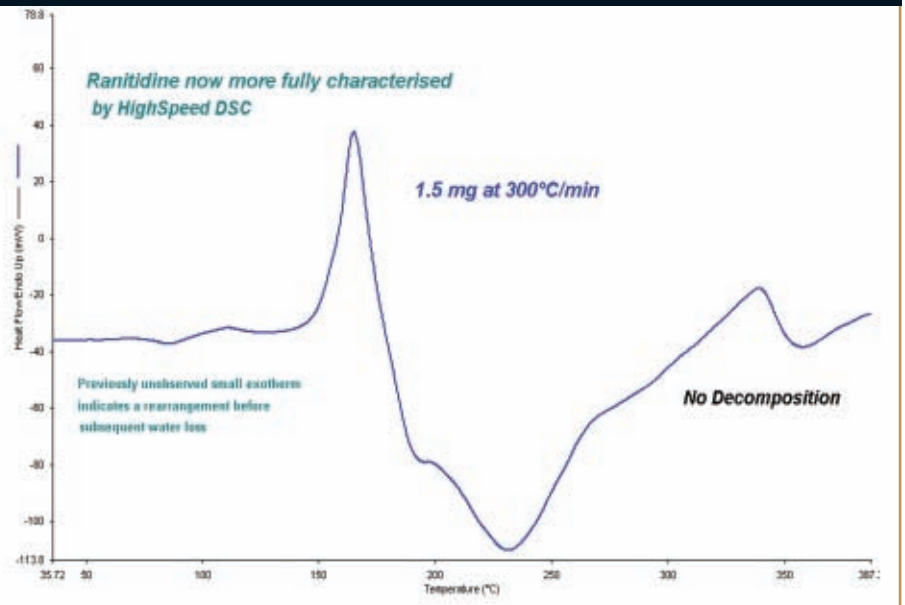
furnace mass, rates of up to 750°C/min can be obtained for quantitative data. This makes Fast Scanning rate DSC very sensitive to the presence of amorphous material in a sample. In addition, high throughput can be achieved as runs typically take less than 1 to 3 minutes. This greatly increases the number of samples one can run in a day. For example, an auto-sampler system running samples at 200°C/min allows up to 268 runs to be done in 24 hours.

Heating at these rates does more than just increase the instrument's sensitivity. It also allows the suppression of kinetic events like decomposition, polymorphic transformations, and reactions by heating and cooling the sample faster than the event can occur. This becomes important when protein concentrations increase as it allows one to collect data before the material decomposes.

PURITY MEASUREMENT

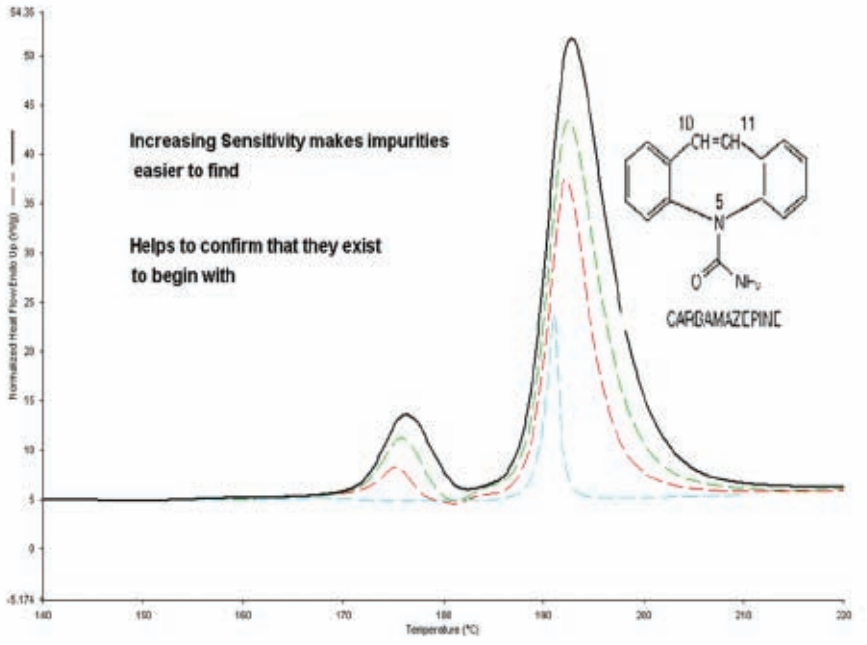
A basic concern in pharmaceutical manufacturing is the purity of the active pharmaceutical ingredient (API) and other materials used in drugs. One quick check on purity is to look at the melting point depression caused by the impurities in the material. Running a small amount (1 to 3 mg) of sample at rates of 200°C/min and up offers several advantages. First, it can shorten run times to under a minute, increasing the throughput of the lab. Second, the increased sensitivity seen in Fast Scanning Rate DSC means less sample is needed. In addition, because decomposition is a kinetic event, decomposition can be pushed to higher temperatures, allowing the onset of melting to be measured before decomposition occurs (Figure 2).

FIGURE 2



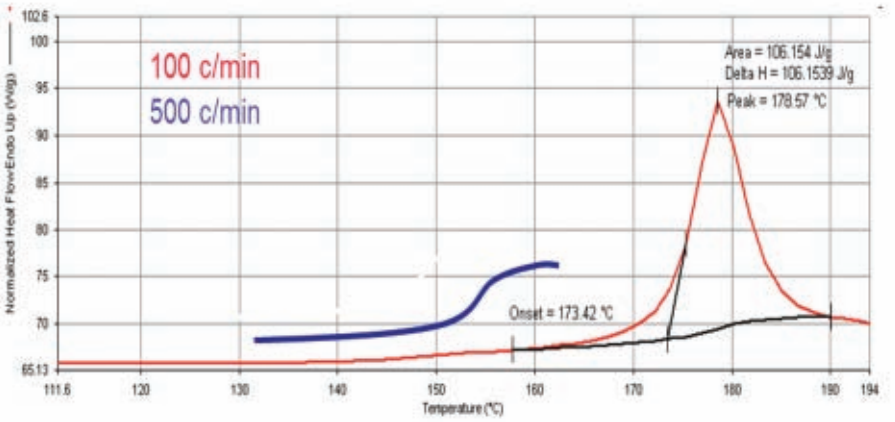
Ranitidane normally decomposes at or just above the melt when run at normal scanning rates. At 300°C/min, decomposition doesn't have time to occur. Courtesy of P. Gabbott, PerkinElmer Thermal Analysis Inc, Seer Green, UK.

FIGURE 3



Snning a sample of Carbamazepine containing 5% Form 3 and 95 Form 1 at rates from 10°C/minute up to 500°C/min. At slow scan rates, the Form 3 converts to Form 1 thermally, and an incorrect ratio of the polymorphs would be obtained. Courtesy of P. Gabbott, PerkinElmer Thermal Analysis Inc, Seer Green, UK.

FIGURE 4



Detection of low levels of amorphous material in samples. A pharmaceutical sample was run by DSC prior to solubility testing and found to contain traces of amorphous material at 500°C/min. This trace amount was not visible at lower rates. Samples run by the author.

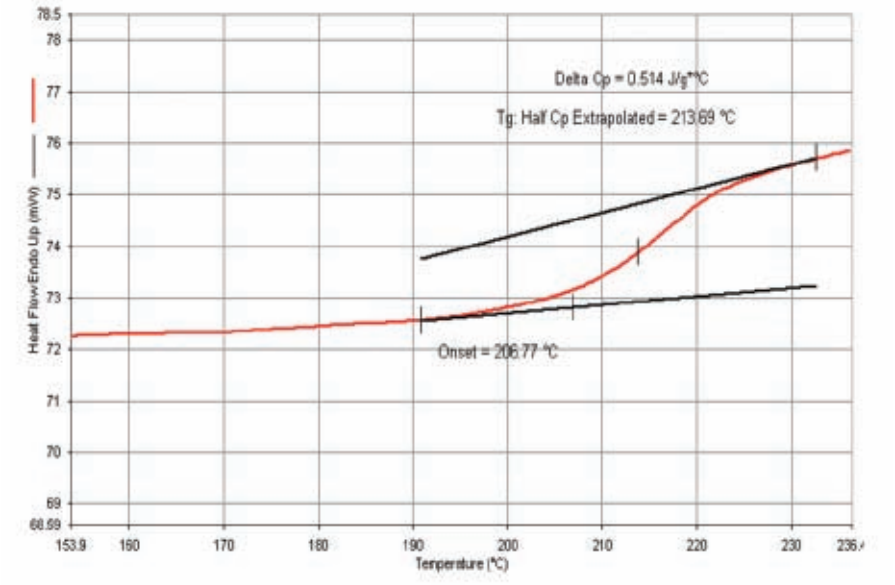
POLYMORPHIC FORMS

Many APIs are used as polymorphic forms of the drug. These forms can be interconverted upon heating and thus what is seen in a conventional DSC run may not represent what is actually present at room temperature. This can cause problems in understanding bioavailability, dose levels, and affect the status of patents. Fast scanning rate DSC's ability to suppress kinetic changes allows one to see the polymorphic form of the material in its original state without having to work back by estimating, which peaks represent transitions (Figure 3).

DETECTION OF WEAK TRANSITIONS

Transitions from many molecules of pharmaceutical interest are weak and diffuse, and conventional DSC methods are often unable to detect them. These samples include lyophilized proteins and excipients: spray dried materials, cellular material, and difficult samples, such as hydroxylethyl starch (HES). Due to the increase in sensitivity seen in Fast Scanning Rate DSC, these transitions become readily detectable at higher rates. This also applies to small quantities of samples, such as materials recovered in vitro from implants or medical devices.

FIGURE 5



The Tg of pure lyophilized bovine serum albumin measured at 200°C/min in the DSC shows a clear transition.

LOW LEVELS OF AMORPHOUS EXCIPIENTS

In most formulations, materials are added to the API to help processing, storage, and delivery. These excipients can be present in varying amounts, and detection and quantification of them is important for QA/QC. Fast Scanning Rate DSC allows us to push detection to levels not previously possible for DSC. For example, the amount of Polyvinylpyrrolindone (PVP), a polymeric

binder, detected by this technique is below 5% whereas both conventional and modulated DSC techniques are limited to a minimum of 40%.

SOLUBILITY CONCERNS

In testing for how well formulations dissolve, the amorphous content can affect how well materials enter solution. Solubility testing is a slow and costly process, so a method of quickly screening for amorphous materials in a supposedly crystalline formulation can be a significant advantage. One of the advantages of the Fast Scanning Rate DSC techniques like HyperDSC is its ability to increase the sensitive of the DSC to the present of weak transitions. When screening materials prior to solubility studies, this increased sensitivity helps one see a low level of amorphous materials that can adversely affect the ability of the formulation to dissolve into a solvent. The presence of amorphous material we detected at rates of 500°C/min is unseen at conventional rates, and run time is a matter of minutes (Figure 4).

LYOPHILIZATION

Lyophilization or freeze-drying is a common technique in pharmaceutical preparation. Running a lyophilized sample for its glass transition temperature by Fast Scanning Rate DSC is relatively simple: a small sample of material, typically 1 to 3 mg, is loaded in a DSC pan and run from 0 to 250°C at 300°C/min. Often, a second run establishes a common heating and cooling history for the samples. Scanning at these rates allows one to measure very weak glass transitions of a sample, such as high protein concentration mixtures as well as pure proteins. In addition, it has been shown that Fast Scanning Rate DSC allows one to scan faster than kinetic events can occur, decomposition is retarded, and a nice clean glass transition results (Figure 5). The appearance of the enthalpic overshoot associated with aging appears unchanged and can still be used for aging studies.

SUMMARY

Fast Scanning DSC can be applied to a wide range of thermophysical measurements used in the modern pharmaceutical laboratory. Because it allows faster throughput and smaller sample sizes, it can reduce testing costs and increase efficiency. The ability to "freeze" kinetic changes in a sample mean that we can, for the first time, be sure what we see in the DSC is what was originally present in the sample and not the product of thermally induced changes. With the great increase in sensitivity of Fast Scanning Rate DSC, materials can now be detected that were previously below the detection limits of DSC.◆

BIOGRAPHY

Dr. Kevin P. Menard, earned his PhD in Chemistry from Wesleyan University and his MBA from Texas Woman's University. He has worked in a variety of industries before coming to PerkinElmer, where he is the Global Business Manager for Thermal Analysis. He has over 150 publications and 14 patents to his credit.

The Impact of Packaging at the Clinical Interface of Vaccine, Healthcare Worker & Patient

By: Brian Lynch, MBA, and Philip Song, MSc

INTRODUCTION

Vaccines are one of the greatest achievements in public health. A recent economic analysis indicated that vaccination of each US birth cohort with the current childhood immunization schedule prevents approximately 42,000 deaths and 20 million cases of disease, with net savings of nearly $14 billion in direct costs and $69 billion in total societal costs.[1]

The success of vaccination, particularly in developed nations, has been based on public recognition of their benefits, access to vaccines, and continuing public and private efforts to promote their use as an integral component of health and preventative care. Despite these successes, opportunities remain to improve vaccination coverage in the US. This is one of the reasons why, in 2010, the National Vaccine Plan was revised and updated to set vaccination goals and strategies, including ensuring a stable supply of, access to, and better use of recommended vaccines in the US.[2] Thus, any way to enhance or improve the systems to help ensure safe and more efficient vaccination should be pursued.

THE EVOLVING VACCINATION SETTING

The vaccination setting in the US is rapidly evolving from the traditional medical home to non-traditional ones, such as retail, schools, and pharmacies. As an example, during the 2010-2011 influenza vaccination campaign, 18.5% of adults received their flu shot in a retail setting.[3] Along with the change in the setting is the change in profile of vaccinators in these new settings with different and varying clinical experience and education. Another reality the immunization enterprise is facing is increasing cost pressures throughout healthcare. Furthermore, all vaccination venues are seeking opportunities to lower the costs of delivering vaccination.

To help ensure consistent, efficient, and cost-effective vaccinations, all means to standardize and simplify the vaccination process should be considered. In this light, the vaccine package - which plays an important role at the clinical interface between vaccine, patient, and caregiver - is increasingly viewed as a critical component of vaccination. Today, there are three types of vaccine packages in use: prefills (PFS), multi-dose vials (MDVs), and single-dose vials (SDVs), each of these with different implications on clinical practice, cost efficiency, and potentially patient outcomes.

EFFICIENCY & PRACTICE IMPLICATIONS - A CLOSER LOOK

A 2010 time-motion study performed by The Johns Hopkins University Bloomberg School of Public Health demonstrated the safety and workflow advantages of PFS.[4] Investigators observed more than 1,500 vaccine injection preparations, and determined time differences and subsequent cost differences associated with the use of PFS versus MDVs. They also observed preparation and handling practices.

Investigators found that preparing a dose using MDVs took 37 seconds longer than with PFS due to the increased number of steps required to prepare a vaccine packaged in a vial. Assuming standard

costs for materials and labor, researchers concluded that administration via PFS could save a clinic approximately $1100 per 1000 doses, assuming the same price per vaccine dose.

More significantly, PFS reduce the risks associated with deviation from best practices as established by the CDC.[5] For example, researchers observed the following with MDVs:

- Neglecting to write on a vial the date it was opened
- Not properly sterilizing the rubber stopper prior to withdrawing vaccine dose
- "Trusting" memory for transcribing lot number
- Pre-drawing the day before or using left-over pre-drawn syringes from a prior day
- Pre-drawn syringes were often left out (not refrigerated) for long periods of time and, in some cases, for a whole day
- Drawing vaccine from multiple vials, especially without checking if the lot numbers are the same[6]

By eliminating many preparation steps required with a vial, a prefilled syringe is simpler and easier to use. Vaccination workflow may be faster and smoother for clinicians and may improve speed of patient throughput.

An additional and important advantage offered by PFS is they come from the (vaccine) manufacturer labeled by the manufacturer. All too often, syringes pre-drawn from vaccine vials are left unlabeled, or are subject to variable labeling practices, clinic by clinic, or perhaps even clinician by clinician. This increases the risk of a wrong or improperly stored injectable vaccine being given; dosing errors also increase when vaccine is prepared and labeled by hand.[7] Prefilled and pre-labeled syringes avoid these errors and omissions, ensure accurate dosing, and offer clinics a ready-to-use safe and simple time-saving alternative to pre-drawing several vaccine syringes in advance.

VARIABILITY IN CLINICAL PRACTICE & POTENTIAL PATIENT IMPLICATIONS

Variations from clinical best practices can be influenced by many different factors, including experience, education, and "real-life" clinician scenarios (multi-tasking, distractions, work-flow pressure, etc). While the vaccine enterprise in the US is considered safe, there have been cases, studies, and data developed that show that errors in preparation and administration can occur.

In 2010, Premier Safety Institute conducted a very large study with over 5,000 clinicians to understand the "current injection practice patterns to assist with targeting outreach and education." This was done in response to "increasing reports of outbreaks in the US involving transmission of hepatitis B and C to patients associated with unsafe injection practices and breakdowns in basic infection control."[8] An example of this occurred in the 2007-2008 influenza campaign when a physician's office in Long Island, NY, was engaged in a practice of drawing six 0.5-ml flu vaccine doses into a 3-ml syringe and subsequently vaccinating six individuals with the same syringe and only changing the needle.[9]

The Premier study revealed that this practice may be more widespread than perhaps anticipated. 0.9% of the clinicians in the survey reported that they change the needle but reuse the syringe on multiple patients. In this same study, 6% of the clinicians also reported using single-dose or single-dose vials for more than one patient, and 1.1% reused a syringe to enter a multi-dose vial and then save that vial for use on another patient.[10]

TABLE 1

Risk Category	Distinct Operations
Contamination of Vaccine	43
Loss of Vaccine Integrity/Stability	26
Wrong Vaccine Dose Administered	25
Wrong Vaccine Administered	17
Expired Vaccine Administered	11

CDC guidelines recommend that healthcare workers use SDVs, syringes, and needles only once, which precludes their use in more than one patient. The study authors wrote, "Our findings provide evidence that healthcare professionals continue to engage in unsafe injection practices, which represent an ongoing threat to patient safety in the US and are devastating to all those patients who are impacted."

THE IMPACT OF VACCINE PACKAGING AT THE USER INTERFACE

"Although there is a clear need for more education, this may not necessarily eliminate all unsafe practices. Adopting principles from human factors engineering, we must consider redesigning devices, equipment, and processes to reduce or eliminate risk of bloodborne pathogen transmission."[11]

This recent statement, which appeared in the *American Journal of Infection Control* is consistent with the FDA's increasing requirements around the integration of Human Factors Engineering (HFE) and device design. HFE is the science and the methods used to make devices easier and safer to use….helping to improve human performance and reduce the risks associated with use.[12]

To better understand the user interface of clinician and various vaccine packages, and the associated potential for errors, a comprehensive study was conducted in 2011 by Interface Analysis Associates.[13] The researchers outlined the process of vaccine preparation from storage through disposal for the three vaccine package types, and then developed a list of all potential errors associated with each step. The study identified all distinct, significant operations within each risk category for potential contribution to risk.

The top five potential risk categories and number of associated potential that could cause them were determined as seen in Table 1.

Furthermore, the study concluded that, in general, the more complex the particular workflow and the more risk factors involved, the more apparent were the benefits of PFS compared with vials. For example, of the 43 distinct operations determined for contamination, both MDVs and SDVs were subject to 38 of these risk opportunities, while PFS were subject to only 23 of them. Similar differences were seen across rest of the top five risk categories.

We can also relate the findings of the study to Six Sigma principles. Six Sigma principles are used to help mistake-proof products and/or processes and rely on the following general approaches:

- Eliminating the possibility of error
- Replacing a risky process with one that is more reliable
- Facilitating or making the task easier to perform
- Detecting errors before carrying out further operations
- Mitigating or minimizing the effects of error

In the user interface study, the number of distinct steps involved in delivering vaccine from the three packaging platforms - up to 50 for MDVs, 45 for SDVs, and 28 for PFS - suggests an advantage to the simpler PFS protocol. By eliminating the number of steps, there is less opportunity to commit an error. For example, PFS have a demonstrated advantage in contamination control because needle changes and drawing drugs from vials (and all the contamination potential those steps entail) do not occur with prefills. Similarly, replacing a highly variable step like syringe filling by a clinician with highly precise aseptic machine filling can help ensure administration of the correct dose, as well as reduce the likelihood of contamination. Finally, opportunities for administering the wrong dose or expired vaccine are minimized by labels being automatically applied on every PFS by the manufacturer. This thereby facilitates the task so it is easier and provides a means of detection as the PFS reaches the end user and point of use with a label. Readily apparent labels also enable corrective protocols to be followed immediately in the event an incorrect drug or incorrect dosage is injected, thus mitigating further effects of the error.

Being pre-labeled, unit-dose, and ready-to-administer, PFS embody "safety-by-design" by their inherent simplicity to use, elimination of several error-prone steps in vaccine preparation and administration, reduced opportunity for syringe reuse and cross-contamination, and assurance of the correct dose with every injection. Clearly printed peel-off labels on vaccine prefills facilitate recording of batch numbers and updating the patient's immunization record.

A MARKET IN TRANSITION

The clinical and workflow benefits of PFS compared with vials rest on the inherent differences required to prepare a dose of a vaccine, or any injectable, packaged in a unit-dose, ready-to-administer format versus a non-ready-to-use format whether single or multi-dose. With their inherently simple design, prefilled syringes do not rely on consistently flawless techniques and aseptic practices to reduce injection-related risks. Instead, they completely eliminate the need for several of the preparation steps that open the door to avoidable risks and consume additional clinician time. In a sense, they embody safety-by-design principles that are important when considering human factors and the user interface.

The growing recognition of the many advantages of PFS have fueled a significant shift toward their use for all vaccine types, most significantly influenza, where the percent of flu vaccine packaged in PFS has grown from about 21% during the 2006-2007 campaign to 48% in 2012-2013.[14] It is worth noting that, in Europe, nearly all of these same vaccines (and vaccine diluents) brought to market are in a PFS package.[15]

Further adoption of vaccines packaged in PFS is expected to continue, for both new and currently marketed vaccines, particularly as clinicians and vaccine enterprise stakeholders look more closely at the implication of packaging at the user interface and understand the benefits PFS offer in terms of greater efficiency and advancing best care. ◆

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BIOGRAPHIES

Brian Lynch, spanning several industries and product technology environments, has over 20 years of marketing management experience. For the past 6 years at BD, Mr. Lynch has been focused on prefillable solutions for both the biotechnology and vaccine market segments. In his current role, he now leads an innovative program to develop and bring health science and technology research to various government, industry, healthcare, and patient organizations on the subject of best care options in vaccine preparation and administration. He earned his BS in Chemical Engineering from Lafayette College and his MBA from the Stern School of Business at NYU. Mr. Lynch can be reached at Brian_Lynch@bd.com.

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DRUG DEVELOPMENT Executive

NOVOZYMES BIOPHARMA: IMPROVING DRUG SAFETY & STABILITY WITH RECOMBINANT HUMAN ALBUMIN

Mark Perkins

Customer Solution Manager

Novozymes Biopharma

"The highly competitive pharmaceutical marketplace is putting pressure on manufacturers to reduce production and processing times, while demand to decrease development costs and speed up time to market are also high on the agenda. As a company, Novozymes has worked to ensure there is an established pathway through the regulatory approval process and that our rAlbumins are manufactured to regulatory standards and deliver a secure supply, with batch-to-batch consistency being of paramount importance."

To ensure the success of drug development programs, pharmaceutical manufacturers must make the correct choice of excipient and excipient supplier. One excipient that has been used widely across the industry for many years is albumin, a natural non-immunogenic plasma protein. Albumin is used extensively in the manufacture of biopharmaceutical, vaccine, and medical device products. In particular, the multifunctional nature of this excipient makes it an attractive tool for stabilizing biopharmaceutical drug candidates because it contributes to reducing aggregation, oxidation, and adsorption during manufacture, formulation, and long-term storage. Traditionally, albumin has been sourced from human or bovine serum. However, due to regulatory concerns over blood-borne contaminants, reliability of supply and performance variability, as well as the quality issues arising from the use of a pooled plasma product, there is a growing demand for more defined, safer, and consistent animal-free albumin products in the industry. Novozymes Biopharma, a leading manufacturer of recombinant ingredients and technologies, has developed a range of high-quality, animal-free recombinant human albumins (rAlbumins) that overcome the formulation and safety challenges associated with conventional sources. Drug Development & Delivery recently spoke with Mark Perkins, Customer Solution Manager at Novozymes Biopharma, to discuss how the company is improving the formulation of many new drugs and offering customers new ways of achieving a competitive advantage.

Q: Can you please provide our readers who may not be familiar with Novozymes Biopharma, some background?

A: Novozymes Biopharma develops and manufactures high-quality, animal-free, and regulatory compliant recombinant ingredients and technologies. We aim to provide pharmaceutical and medical device manufacturers with solutions that help them address the industry's most common challenges in developing innovative, safe, and consistent products. The company has a number of large-scale manufacturing facilities worldwide, which are all run to cGMP Q7 quality standards to ensure customers receive the highest level of product quality and consistency, as well as the security of long-term supply. Throughout the company, we have a customer-integrated approach and combine our scientific know-how and the specific needs of our customers to deliver improved products and performance.

Q: How is Novozymes working with its customers to enhance the formulation of their products?

A: To ensure a drug candidate is safe to administer and retains the appropriate activity, it must be formulated in a manner that confers physical, chemical, and biological stability. However, developing new or redesigning existing therapeutics with these attributes is a time- and resource-consuming procedure, the success of which cannot be guaranteed. Increasing pressure is therefore being placed on manufacturers to implement improved drug formulation processes. At Novozymes, our primary focus is on developing and producing recombinant products and technologies that offer superior safety and performance to our customers. We do this by providing access to high-quality ingredients, proprietary technologies, and unique know-how, contributing toward the development of improved therapeutic treatments, providing real and sustainable benefits to both manufacturers and patients.

As a company, we are constantly reviewing industry trends and looking for new opportunities to improve our customers' processes by developing better and safer alternatives to the products that they are currently using. However, we are more than just a supplier of enabling technologies or products; we see our relationship with each customer as an individual partnership. By combining our scientists' and researchers' unique understanding of our biological solutions with customers' specific application knowledge, we work with customers to deliver solutions that solve their most demanding challenges.

Q: What differentiates Novozymes' rAlbumins from alternative technologies?

A: At Novozymes, we understand the needs of the pharmaceutical industry and have designed our rAlbumin products, Recombumin® and Albucult®, to meet the highest quality standards. They have been developed and optimized to deliver a stable, safe, and regulatory-compliant ingredient for the medical device, drug delivery, and formulation markets. Expressed in a proprietary *Saccharomyces cerevisiae* expression technology, Recombumin and Albucult have been developed to deliver quality and unmatched performance benefits in our customers' applications, including drug and vaccine manufacture, device coating, IVF media, specialized cell culture, and cell therapy applications.

Recombumin, which was the world's first commercially available, GMP-manufactured, animal-free rAlbumin was developed specifically as a drug and vaccine ingredient. The product is already being used with excellent results by a number of large pharmaceutical companies and has been approved for use in the manufacture of the FDA- and EMA-approved MMR™ II childhood vaccine from Merck and Co. The product is also currently under evaluation as an ingredient in several other drugs undergoing clinical development in the US and EU. We believe our rAlbumins are the market-leading products for the pharmaceutical industry and deliver unprecedented performance benefits to our customers' applications. As a result, more rapid development of safe and stable formulations of even the most difficult drug candidates can be achieved.

Q: What is it about Novozymes' rAlbumins that enable them to significantly improve drug formulations?

A: Excipients such as albumin are vital components of a pharmaceutical formulation; contributing significantly to the functionality and stability of the final formulation. As a result, there is a strong relationship between the quality attributes of an excipient and its performance in the finished product. In the past, the quality aspects of an excipient have come second to the active ingredient. However, conventional excipients have been proven to suffer from performance

inefficiencies, particularly when it comes to the stabilization of complex small molecules, proteins, and peptides. In addition, excipients from different vendors and sources may exhibit significant variability in their functional and physical properties. Recent years have also seen the regulatory landscape evolve considerably, along with greater business needs for faster "risk-free" drug development processes, meaning there is high demand for well-defined excipient products that offer superior features with respect to protein purity, protein homogeneity, and functional characteristics.

At Novozymes, we have designed our rAlbumin products to meet the highest quality standards and offer superior functional and physiochemical properties, as well as improved pharmacokinetic attributes. In addition to providing solutions that help our customers make their products safer and more effective, we also recognize that therapeutic proteins need to be formulated to provide optimal stability during manufacturing processes, transportation, and storage. For that reason, our scientists have worked for many years to prove that our rAlbumins function as effective multipurpose excipients, which have been shown to stabilize proteins or live viruses by preventing aggregation, oxidation, or adsorption. The use of a single or reduced number of excipients not only simplifies the formulation strategy for pharmaceutical manufacturers but also accelerates development time.

Q: Can you explain how Novozymes' rAlbumins help to reduce time to market and speed up the approval process for customers?

A: The highly competitive pharmaceutical marketplace is putting pressure on manufacturers to reduce production and processing times, while demand to decrease development costs and speed up time to market are also high on the agenda. As a company, Novozymes has worked to ensure there is an established pathway through the regulatory approval process and that our rAlbumins are manufactured to regulatory standards and deliver a secure supply, with batch-to-batch consistency being of paramount importance. By ensuring regulatory compliance and consistency, we can reduce processing and testing times for our customers to drive product efficiency. As Novozymes' rAlbumins are also animal-free, we are well positioned to help our customers' dealings with regulatory authorities where transmissible spongiform encephalopathies (TSE) are a particular issue.

All of Novozymes' rAlbumins are manufactured to cGMP standards in large-scale facilities and omit the use of any animal- or human-derived materials. As such, they are the only cGMP products available that meet the standards published by the United States Pharmacopeia and are supported by a strongly documented safety package and drug master file. As a company, we have over 20 years of experience in providing experienced, technical, product, and regulatory support, tailored to each customer's individual needs. Our dedicated team of R&D, manufacturing, and regulatory experts have unparalleled knowledge in working with albumin and regulatory agencies, such as the FDA and EMA, and can provide specialist support for our customers applications and product design. These capabilities help to significantly speed up regulatory approval processes and helps improve the efficiency in getting our customers' final products to market. By sharing our in-depth product and technology knowledge in this way, we aim to provide a level of technical support that surpasses our customers' expectations on all levels.

Q: Can you tell us some of the interesting applications for which your customers are using rAlbumins?

A: Globally, our customers are using Novozymes' rAlbumins to develop superior products that offer unique points of differentiation in highly competitive marketplaces. A number of our customers are evaluating the products for the development of liquid-stable protein therapeutics because the stabilizing effect from albumin may exceed those conferred by conventional sugars, amino acids, and detergents (SADs). In the medical device sector, Novozymes' rAlbumins have delivered customer product superiority and ease of approval in addition to security of supply. This has enabled partners to reliably commercialize their products with peace of mind when it comes to the ongoing availability of key ingredients. By being manufactured to regulatory standards to deliver a secure supply, consistency, and increased efficiency, our rAlbumins offer customers a compliant albumin alternative. ◆

Company Profile

Aptalis Pharmaceutical Technologies
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Website: www.AptalisPharmaTech.com

Aptalis Pharmaceutical Technologies (formerly Eurand Pharmaceutical Technologies) specializes in product development that leverages our proprietary pharmaceutical technologies including Customized Drug Release, Bioavailability Enhancement, and Taste Masking for ODTs and other dosage forms. In collaboration with our partners, we utilize these technologies to develop and distribute novel prescription and OTC products that are designed to have advantages over existing products and address unmet medical needs. We have a multinational infrastructure with integrated R&D and manufacturing facilities in the US and Europe, allowing us to offer global solutions to companies in various regions around the world. We are proud of our successful quality inspection rates across our multiple facilities, which are audited annually by the various regulatory bodies.

Our capabilities include formulation through to scale-up, thereby enabling commercial-scale manufacturing of the products we develop for our partners, in addition to securing IP protection for new commercial entities created from the use of our proprietary technologies.

Customized Drug Release Technology Platform

The Customized Drug Release technology platform consists of a range of technologies that provide a wide variety of customized release profiles that may be tailored to optimize a drug's therapeutic performance by improving its efficacy, enhancing its safety, or reducing the frequency of its dosing, thus improving patient acceptability and compliance/adherence to the resulting product.

Bioavailability Enhancement Technology Platform

We offer technologies that can improve the bioavailability of drugs that have low aqueous solubility and for those that have an extreme pH-dependent solubility profile. The resulting formulations can then provide effective oral dosing of poorly soluble drug candidates, equivalent therapy at lower doses, faster onset of action, and/or minimization of food effect.

Taste Masking Technology Platform

The application of our proprietary taste-masking technologies converts unpleasant tasting APIs into products with a pleasant taste and excellent mouth-feel for improved patient appeal, and is available in a variety of presentation forms including our ADVATAB® Orally Disintegrating Tablets (ODTs).

We have established partnerships with some major pharmaceutical companies, and our track record of commercialization success includes products that are marketed in more than 50 countries around the world. Established collaborative partnerships include companies such as Pfizer, Johnson & Johnson, Sanofi, Novartis, Bayer, Watson, Abbott, GSK, Eisai, Teva, Bristol-Myers Squibb, and others.

Through our collaboration agreements, we also offer licensing opportunities of existing prescription and OTC products across a range of therapeutic categories. These therapeutic categories include but are not limited to: gastrointestinal, cardiovascular, pain, nutrition, respiratory, and CNS indications. These products are designed to meet regulatory requirements for approval in a number of markets around the world.

Visit us at **www.AptalisPharmaTech.com** to view our current product portfolio available for out-licensing and learn more about our full service co-development capabilities leveraging our technologies.

AVEVA DRUG DELIVERY SYSTEMS, INC.

TRANSDERMAL PATCH EXPERTS

3250 Commerce Parkway
Miramar, FL 33025
T: 954-624-1374
Website: www.avevadds.com
Contact email: Robert.bloder@avevadds.com

AVEVA Drug Delivery Systems Inc.

is a global leader in transdermal drug delivery located in the United States. The company has an extensive history of providing pharmaceutical partners with fully integrated, controlled-release transdermal products that fulfill unmet market needs or supply high-quality, affordable brand equivalents. By leveraging this experience, AVEVA offers a full range of research, development, and manufacturing capabilities to produce transdermal pharmaceutical products that can improve the quality of life, usage, and compliance rates for patients.

A Higher Level of Performance

That's the promise of Aveva Drug Delivery Systems, combining innovation and unparalleled industry experience to advance drug delivery and pioneer new frontiers in transdermal drug delivery for new chemical entities and life cycle management opportunities to enhance existing products.

Aveva transcends traditional limitations of patch technology and business partnerships to achieve new levels of product and corporate performance.

- Customizing solutions to the unique characteristics of each drug
- Masterfully balancing the patch properties of adhesion reliability and gentleness that lead to an enhanced patient experience
- Transdermal candidate assessment of APIs in as little as four weeks

Aveva implements a flexible, customer-oriented business philosophy that adds value to projects and exceeds customers' expectations.

For more information, please contact Robert J. Bloder for:

***Product & Pipeline Licensing Opportunities**
***Joint Ventures & Co-Developments**

TRANSDERMAL TRANSCENDENCE

A higher level of performance

Delivers new possibilities

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- **Turnkey GMP Operations**
  - From product feasibility to commercial supply
  - Decreased tech transfer risk
- **AVEVA Offers**
  - Proprietary pipeline and approved product licensing
  - Co-development & Joint Venture opportunities
  - Full range of R&D and manufacturing

AVĒVA
DRUG DELIVERY SYSTEMS

That's the promise of Aveva Drug Delivery Systems, combining innovation and unparalleled industry experience to advance drug delivery and pioneer new frontiers in transdermal drug delivery for new chemical entities and life cycle management opportunities to enhance existing products.

As a global leader of transdermal patches offering a full range of research, development and manufacturing capabilities, Aveva transcends traditional limitations of patch technology and business partnerships to achieve new levels of product and corporate performance.

- Customizing solutions to the unique characteristics of each drug
- Masterfully balancing the patch properties of adhesion reliability and gentleness that lead to an enhanced patient experience
- Transdermal candidate assessment of APIs in as little as four weeks

A flexible, customer-oriented business philosophy that adds value to projects and exceeds customer expectations

To license a product or to see how we can add value to your project, call Robert J. Bloder, Vice President Business Development, at **954.624.1374** or visit **www.AvevaDDS.com**

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Fax: 1.847.948.4770 Email: biopharmasolutions@baxter.com
Website: www.baxterbiopharmasolutions.com

Industry Leader with Global Presence

Baxter has more than 80 years of parenteral contract manufacturing experience with over 50 manufacturing facilities across six continents. BioPharma Solutions, a business unit of Baxter Healthcare, works with pharmaceutical companies to support their commercialization objectives by providing scientific expertise, sterile manufacturing solutions, parenteral delivery systems, and customized support services needed to meet the unique challenges that parenteral products face. BioPharma Solutions is a leading contract manufacturer of prefilled syringes in North America and named the "Best Contract Manufacturing Organization" at the Vaccine Industry Excellence Awards, three years consecutively (2010, 2011, 2012).

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. BioPharma Solutions offers a dedicated facility that utilizes experienced operators, sophisticated equipment and systems, and robust standard operating procedures, training and risk assessments. Our contract manufacturing services provide customers access to world-class scientific expertise, state-of-the-art facilities, and processes designed to help ensure a reliable supply of quality product to the market. Baxter is the only company worldwide with facilities certified by SafeBridge doing both parenteral drug substance synthesis and parenteral drug product manufacturing and testing.





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

BioPharma Solutions

The Promise of Science Formulated

Experience Makes the Difference

With 80 years of parenteral expertise, we can help to navigate the pathway of success for your molecule. We can help you overcome technical challenges, including process and formulation development, technology transfer, and analytical methods development. Our scientific teams are skilled in the development of solutions, suspensions, and freeze-dried dosage forms to help optimize product quality throughout manufacturing. BioPharma Solutions provides our clients with confidence of delivery, service, and integrity—we know the work we do is ultimately **vital to the patients you serve.**

For more information, visit
baxterbiopharmasolutions.com
or email us at
biopharmasolutions@baxter.com

Baxter

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E: solutions@catalent.com
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 worldwide clinical and commercial supply capabilities for drugs, biologics and consumer health products. With over 75 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 markets, including 49 of the top 50 pharmaceutical and 41 of the top 50 biotech companies. Our team of over 1,000 talented scientists has supported more than half of innovative drug and biologic approvals since 2004, and we have more than 450 active development programs for new customer products. We have 18 development teams in 10 markets. Our 25+ global sites serve over 1,000 customers in over 80 countries supplying more than 60 billion units 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. Our robust GPEx® mammalian cell line engineering technology accelerates large molecule drugs from discovery to clinic and our unique Optiform™ technology 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.

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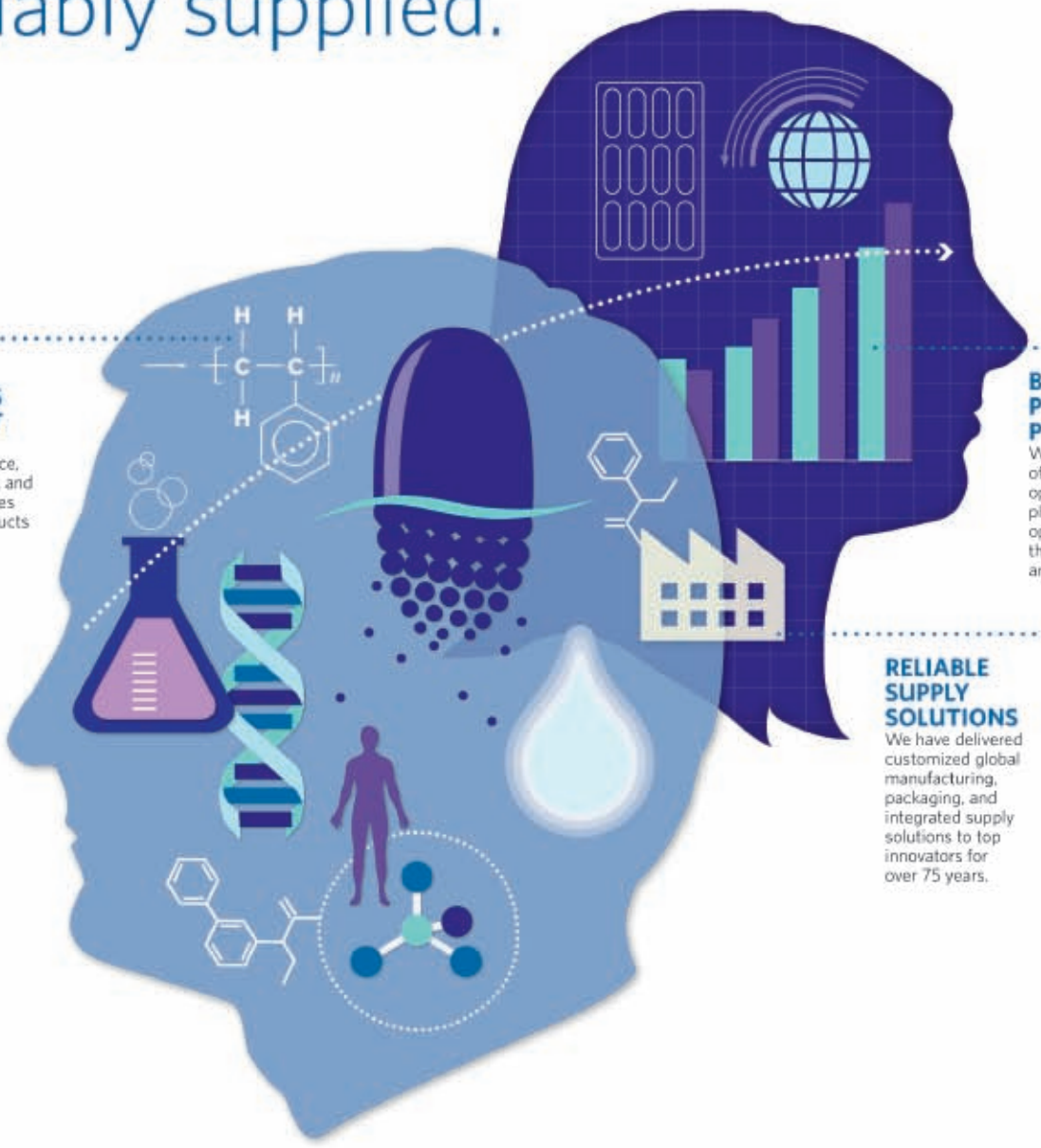
reliably supplied.



MORE MOLECULES TO MARKET
We provide the broadest experience, deepest expertise, and unique technologies to take more products to market, faster.

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With a wide range of formulation options and delivery platforms, we can optimize your product's therapeutic benefits and marketability.

RELIABLE SUPPLY SOLUTIONS
We have delivered customized global manufacturing, packaging, and integrated supply solutions to top innovators for over 75 years.

Catalyst + Talent. Our name combines these ideas. With our broad range of experience and deep expertise, we have the talent and unique technologies to transform your concepts into excellent results. From drug and biologic development services to delivery technologies to supply solutions, we are the catalyst for your success. Whether you are looking for a single solution tailored to your needs or multiple answers throughout your product's lifecycle, we improve the total value of your treatments—from discovery, to market, and beyond.

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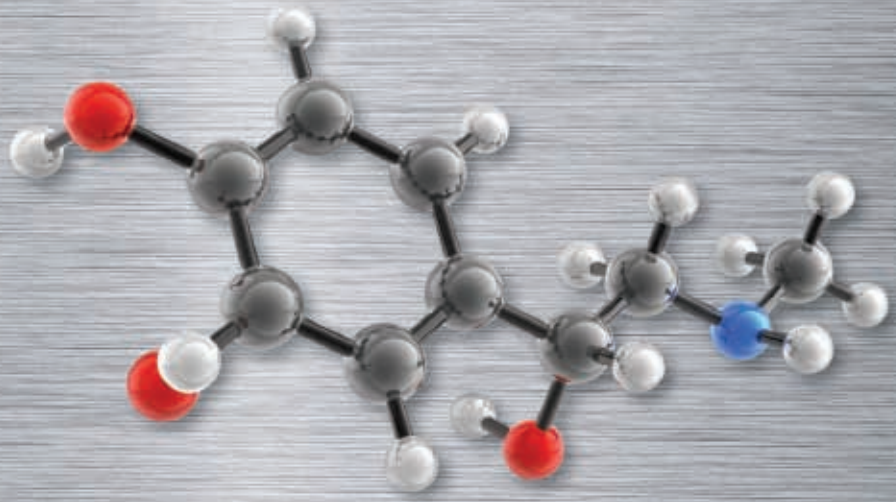

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Faster to First-In-Human

The easy and reproducible method to manufacture nanoparticles, nanoemulsions, nanosuspension, and liposomes to accelerate the pace to First-In-Human, with Covaris Adaptive Focused Acoustics (AFA™).

Covaris Adaptive Focused Acoustics technology offers a breakthrough process for forming nanosuspensions of early stage API formulations. A scalable, self-contained, isothermal process, AFA™ enables the formation of nanosuspensions with a very limited amount of material. While suspension volumes as low as 100 microliters are possible, the AFA™ process can also scale-up to liter volumes for preclinical animal studies and First-in-Human (FIH) trials.

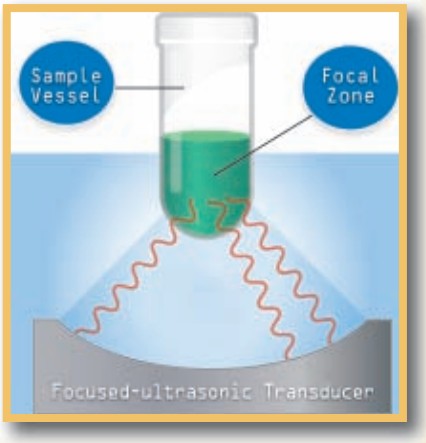
AFA™ has been utilized on a number of proprietary and generic compounds, using low concentrations of standard excipients, to achieve particle sizes smaller than alternate technologies, such as bead/ball milling or high pressure homogenizers. With the capability to produce a Best in Class particle size in a non-contact, self-contained vessel with 100% material recovery, AFA® dramatically reduces the development time to FIH trials. More important, AFA™ can allow an early stage compound to move forward into development that might have otherwise been dropped due to limited material availability. Indeed, AFA™ may be the ONLY solution for preparation of small scale nanosuspensions in a closed, sterile vessel without the risk of bead contamination.

Liposomes

Corvaris AFA™ is the method of choice to manufacture lipid based nanoparticles for drug delivery. With AFA™, liposomes are produced without the use of solvents and at low temperature independent of the lipid phase transition temperature. This method allows for easy miniaturization of liposomes formulation, yet it scalable to any batch size required as it scales to a true continuous process flow with PAT feedback.

A liposome based formulation is formed by combining the liposome components: lipids, buffer, and molecule of interest bioactive into a single closed vessel and processing with a Covaris Focused-ultrasonicator. Liposome size and distribution are controlled via the AFA™ process settings. Note that ORGANIC SOLVENTS ARE NOT A REQUIREMENT, and the liposome forms at a LOW SAMPLE TEMPERATURE, significantly reducing the risk of degrading delicate molecules, such as biologics and others which may be sensitive to temperature and solvents.

With the ability to dramatically reduce time to FIH, enable evaluation of scarcely available materials, and manufacture liposomal formulations without damaging thermal-sensitive active components, Covaris Focused-ultrasonicators offer a breakthrough for development of Drug Delivery Systems and Formulations.
For more information contact us at 781.932.3959 or visit us at www.covarisinc.com.



Company Profile

DPT Laboratories
318 McCullough Ave.
San Antonio, TX 78215
T: (210) 476-8100 F: (210) 829-8733
Web Site: www.dptlabs.com

Company Background: Date Founded: 1938
Number of Employees: 1,000

Company Description: With a specialized focus on semi-solids and liquids, DPT offers pharmaceutical companies the broadest range of capabilities in the industry. From R&D formulation to commercial-scale manufacturing, small batches to large, liquids to emulsions, cans to pumps, sterile or non-sterile, we offer clients of all sizes the most effective resources for meeting challenges.

And since semi-solids and liquids are the only thing we do, we have an unmatched level of scientific and engineering expertise - particularly when it comes to tackling unique projects and overcoming development and manufacturing challenges - and a good track record with the FDA. We also have a very stable employee base, giving us a wealth of institutional knowledge and the ability to be responsive to client requirements.

Whether you're a start-up operation or Big Pharma, we can take your project all the way from lab to production.

Just as important, we continue to invest heavily in our capabilities, including centers specializing in semi-solid and liquid manufacturing, aseptic manufacturing and R&D.

Our focused approach and extensive experience makes our operations extremely efficient, and gives us the foresight to plan effectively for each project's needs.

Services & Capabilities

Development

- Formulation Services
- Analytical Services
- Packaging
- Process Development
- Stability Studies
- Microbiology
- Clinical Trial Materials
- Regulatory Submission
- Inhalation Product Testing

Manufacturing

- Semi-solids & Liguids
- Sterile Products
- Aerosol Foams & Sprays
- Metered-Dose Inhalers (pMDIs)
- Site and Technical Transfers

Facilities

Each of DPT's three Centers of Excellence is staffed with experts who provide pharmaceutical development and manufacturing services dedicated to its respective specialty:

The Center of Excellence for Research and Development offers comprehensive development services and customized solutions for sterile and non-sterile semi-solid and liquid dosage forms.

The Center of Excellence for Semi-Solids and Liquids provides solutions for both clinical and commercial-scale manufacturing according to current Good Manufacturing Practice (cGMP) guidelines. This center also includes a dedicated aerosol and pressurized Metered-Dose Inhaler (pMDI) manufacturing facility.

The Center of Excellence for Sterile and Specialty Products specializes in the development and aseptic manufacturing of clinical trial materials and commercial-scale products that meet the most stringent sterile pharmaceutical requirements.

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Maryland Heights, MO 63043
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F: (314) 344-9934
Website: www.eaglabs.com/ls

Evans Analytical Group (EAG),

founded in 1978 as Charles Evans & Associates, has grown to be one of the most highly specialized analytical service organizations operating in the medical device and pharmaceutical fields. EAG initially focused on providing services to the semiconductor and electronic manufacturing industry, but quickly diversified into other areas, where knowledge and understanding of materials' property, stability, and purity are of critical importance, such as in the area of drug development, packaging, and delivery. The company has two divisions that provide direct services to the pharmaceutical industry:

Materials Characterization

With sites across the US, including NJ, MN, MO, and CA, the Materials Characterization division of Evans Analytical group focuses on supporting R&D and failure analysis. Services of interest include: electron microscopy (both SEM and TEM) for imaging materials; FTIR and Raman spectroscopy for organic materials identification; TOF-SIMS and XPS/ESCA for extremely sensitive surface analysis, determination of chemical state, and chemical imaging; XRD for studies of crystal structure; ICP-MS and IC for elemental analysis; and all types of chromatography for organic materials purity determination.

EAG Life Sciences

The EAG Life Sciences division focuses on the specialized analytical needs of the pharmaceutical industry. This contract research organization (CRO) is FDA registered, cGMP compliant, and DEA registered. Services of interest include method development and method validation, extractables and leachables studies, stability services, bioanalytical services, physical testing, quality control testing, custom synthesis, and specialized drug-device testing.

Further services available from EAG in other divisions include testing of electronics and electronic components (Release to Production services) and environmental fate studies of chemicals and agrochemicals (EAG AgroSciences).

Across divisions, EAG works extremely closely with its customers to design a specific service or combination of services to meet that customer's needs. These services may range from a short 1-hour identification of an unknown material discovered during R&D, to multi-month FDA-compliant stability studies.

EAG is also highly active supporting its clients in IP protection and litigation. At either end of these service scales, EAG uniquely enables direct person-to-person access to the scientists and analytical chemists who actually produce the data and reports in the laboratory. This close access allows direct insights to be obtained into the samples and issues at hand.

With a combined staff of over 500 globally, and a unique combination of instrumentation and expertise, EAG is well placed to help companies of all sizes in any location to meet their goals in relation to R&D; bringing new product through approval process; and ultimately to market.

FOSTER DELIVERY SCIENCE

FOSTER DELLIVERY SCIENCE
45 Ridge Road, Putnam, CT 06260
T: (860) 630-4525
Contact: Brittany Palmer
E: bpalmer@fostercomp.com

Foster Delivery Science is a full service contract research and manufacturing firm specializing in hot melt extrusion (HME) of active pharmaceutical ingredients (APIs) for oral dosage forms, transdermal and transmucosal films, and implants.

Comprehensive Hot Melt Extrusions Services

Foster Delivery Science has over 20 years of experience in melt extrusion for life science applications. Our cGMP facility is equipped with state-of-the-art melt extrusion equipment to support pharmaceutical clients. We offer complete services throughout the product life cycle:

- Formulation – Material Selection
- Feasibility – Small Batch Production
- Process Development – Non-GMP Process Definition
- GMP Trials – Clinical Supply
- Scale-Up – Maximization of Throughput
- Validation – Process & Test Methods
- Production – Implement Manufacturing Protocols

Range of Dosage Forms

Foster's inventory of downstream processing equipment is available to manufacture traditional and customized dosage forms:

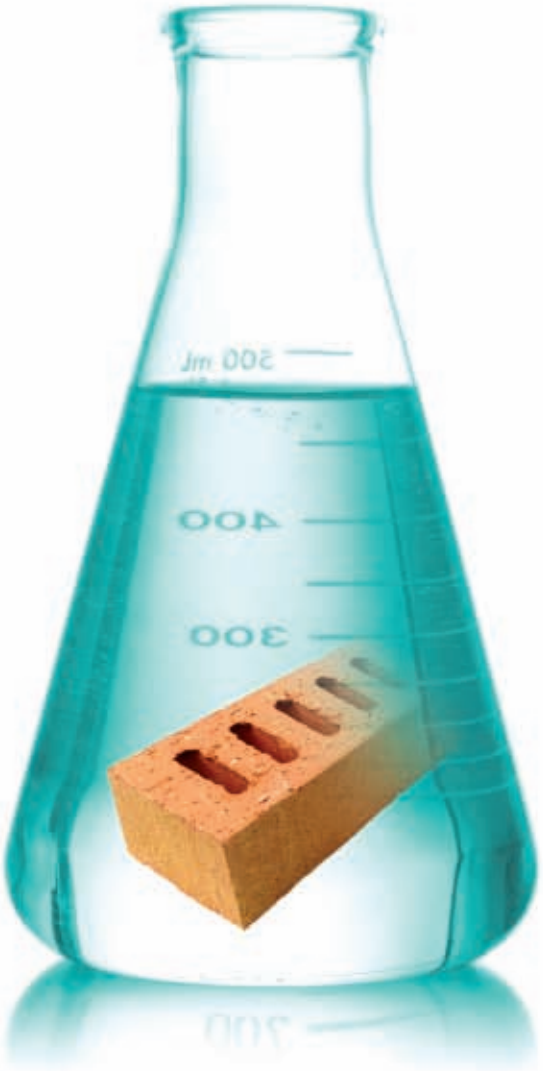
- Tablets & Tablet Coating
- Pellets & Spheres for Capsules
- Pellets & Micro Pellets
- Films (Transdermal & Transmucosal)
- Fibers & Monofilaments
- Intra Uterine Devices
- Implants
- Customized Dosage Forms

Quality & Regulatory

At Foster, we believe that drug product development and manufacturing begins with a total commitment to quality. Our quality and regulatory systems represent our commitment to every phase of our business. This commitment is a foundation in our corporate culture and demands quality in every service we offer and every system our business is built on.

Certifications & Registrations

- cGMP
- ISO 9001: 2008
- ISO 13485: 2003
- CSL Registration
- FDA Registration



Hot Melt Extrusion

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FEATURED KEYNOTES

HEALTHCARE AND POLICY

Billy Tauzin
Former **U.S. Congressman**,
Former President and CEO
PhRMA

INDUSTRY

David Pyott
Chairman, President and CEO
ALLERGAN

INNOVATION

Myshkin Ingawale
Inventor, co-founder
BIOSENSE TECHNOLOGIES

KEYNOTE PANELS

Where Does Drug Delivery Fit into the Pharmaceutical Pipeline?
PARTICIPANTS FROM **Pfizer · Bayer Pharmaceuticals · Sun Pharmaceuticals · Astrazeneca · Sandoz**

How Has the Political Climate Affected Drug Development and Delivery and How is the Industry Coping?
PARTICIPANTS FROM **Allergan · Phrma · Express Scripts · Johnson & Johnson · Pfizer**

Drug Delivery Devices: How Are Devices and Combination Products Changing the Game?
PARTICIPANTS FROM **Merck · Sanofi-Aventis · Bd Medical - Pharmaceutical Systems · Genentech · Eli Lilly & Company**

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– Christopher Jordan, Co-Founder and President, JRX Biotechnology Productions, Inc

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FROST & SULLIVAN

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

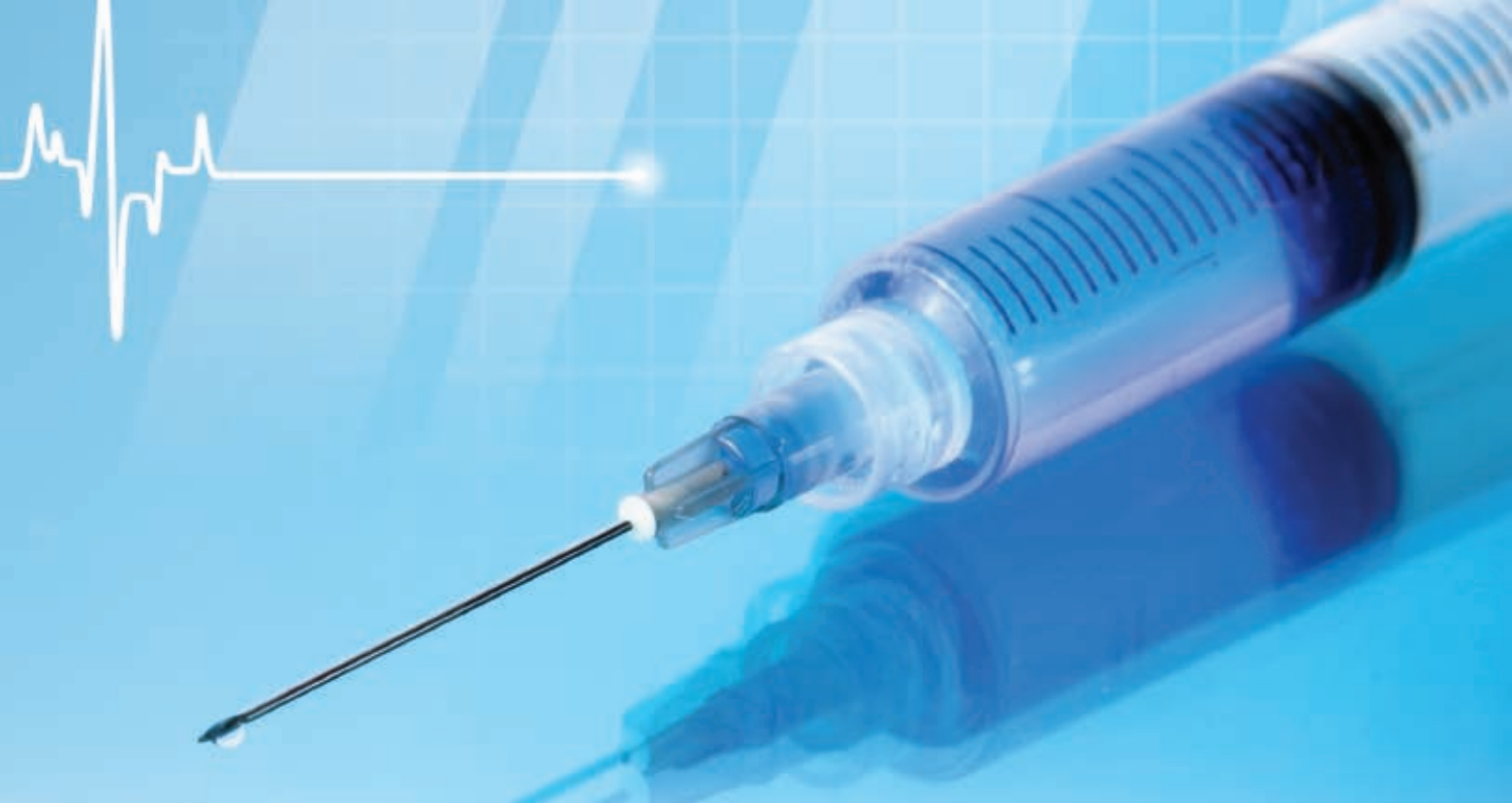
Drug delivery technologies are a viral component of the dynamic Life Sciences industries, but how well does your company understand the end-user's perspective on desired attributes, compliance issues and drivers of adoption/non-adoption for different drug delivery types?

Frost & Sullivan's Life Sciences experts can provide your organization with the research and tools necessary to fully understand your customers as well as identify and take advantage of the best opportunities for growth in the drug delivery technologies market.

Our expert healthcare analysts:

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

For more information on how to find growth opportunities in the drug delivery market, please contact Britni Myers at britni.myers@frost.com or **210.477.8481**.



Exclusively Focused on Growth	Actively engaged in identifying new market opportunities, researching competitive strategies and developing implementation plans that enable clients to accelerate growth.
Industry Breadth	Cover the broadest spectrum of markets and technologies to provide clients with the ability to look outside the box and discover new and innovative ideas.
Global Perspective	More than 40 global offices ensure that clients receive global coverage and perspective based on local and regional expertise.
Continuous Monitoring	Continuously monitoring markets, technologies, careers and geographies for growth opportunities.
CEO's 360 Degree Perspective™	Disciplined research integrates all critical research methodologies to significantly enhance the accuracy of decision-making and lower the risk of implementing growth strategies.
Trusted Partner	Work closely with executive teams to leverage all of Frost & Sullivan's expertise to promote revenue-generating initiatives.

Frost & Sullivan, the Growth Partnership Company, works in collaboration with clients to leverage visionary innovation that addresses the global challenges and related growth opportunities that will make or break today's market participants. For more than 50 years, we have been developing growth strategies for the global 1000, emerging businesses, the public sector and the investment community. Is your organization prepared for the next profound wave of industry convergence, disruptive technologies, increasing competitive intensity, Mega Trends, breakthrough best practices, changing customer dynamics and emerging economies?

COMPANY PROFILE

GATTEFOSSÉ USA
115 West Century Road, Suite 340
Paramus, NJ 07652
T: (201) 265-4800
Website: www.gattefosse.com

Company Profile

Gattefossé is a leading provider of multi-functional excipients and formulation solutions to health industries, worldwide.

Gattefossé specializes in the transformation of Oleochemicals natural ingredients lipids into sophisticated excipients of pharmaceutical quality. Our products are engineered to address drug delivery issues for all types of dosage forms. Gattefossé is a pioneer in microemulsions (SEDDS, SNEDDS), bioavailability enhancers, sustained release vehicles, emulsifiers, solubilizers, lubricants, and processing aids for a wide range of applications.

Core Values

The blue print for the company's success and global status is entrenched in the company history of 130 years and a corporate culture that is based on:

- Responsiveness to the rapidly evolving market needs;
- Commitment to quality of service aiming to meet and surpass customer expectations;
- Maintaining an innovative edge by investing in education and research;
- Support for professional associations and scientific meetings; and
- Providing care for the under-privileged pockets in the global village.

Formulation Solutions

We provide solutions for oral, topical, transdermal, and other routes of administration.

Gattefossé products and technologies are commonly found in currently marketed medicines. More recently, they are considered in development of novel dosage forms. Applications include well-established formulation techniques, including direct compression; wet or melt granulation; spray congealing; solid lipid nanoparticles; solid dispersions, emulsions; nanoemulsions; and solutions.

Technical Support

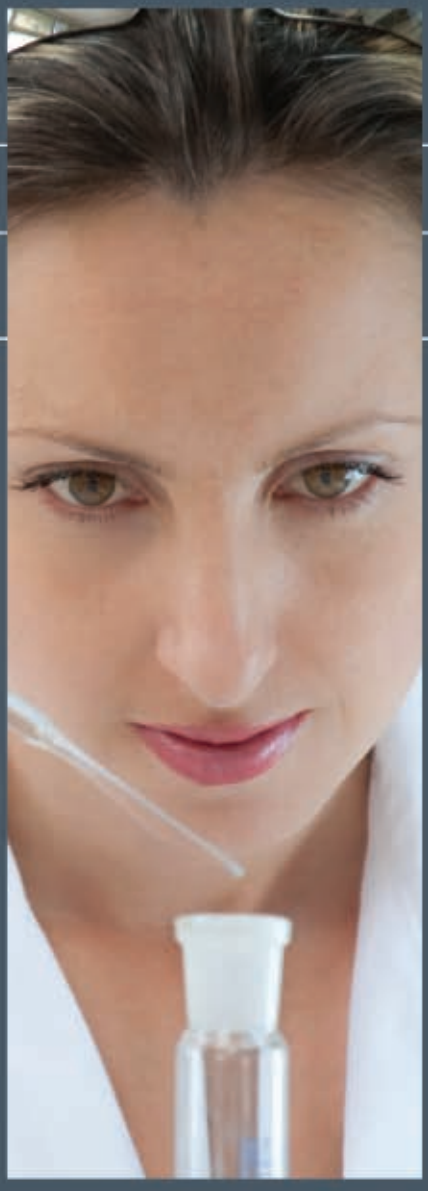
Our scientists and regulatory experts work diligently to provide not only formulation guidelines but also extensive safety data, quality documentation, and proof of regulatory compliance in USA, Europe, and Asia. Gattefossé is fully committed to providing product support documentation for drug filings that involve our excipients.

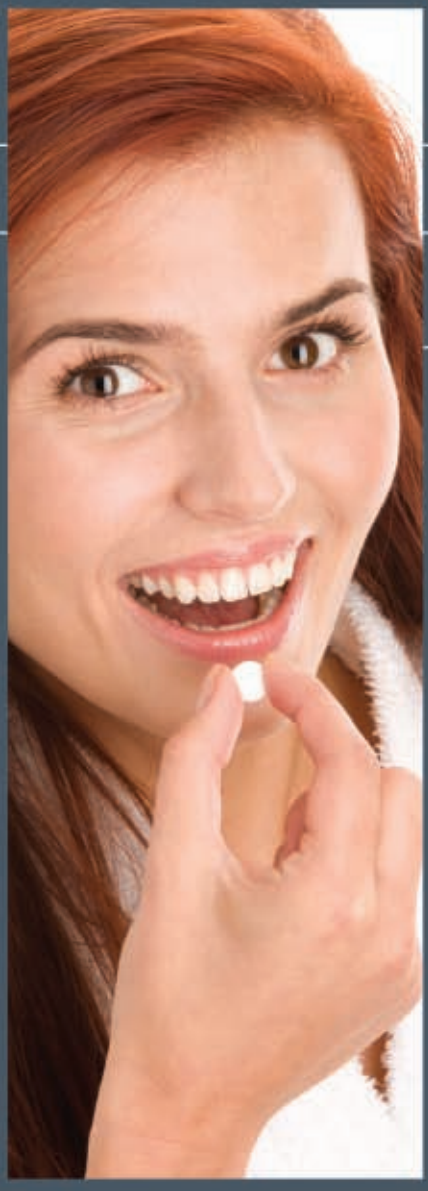
Gattefossé has an extended network of affiliates and distributors in more than 60 countries. To find your local representative, simply visit gattefosse.com.

From United States and Americas, simply dial (201) 265-4800 or write to info@gattefossecorp.com.

GATTEFOSSÉ

OUR EXCIPIENTS... YOUR DELIVERY SOLUTIONS





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201.265.4800 ~ info@gattefossecorp.com

GRÜNENTHAL
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52078 Aachen, Germany
T: 011 49 241 569 0
Website: www.grunenthal.com

Strong Commitment to Innovation

Grünenthal is one of the last remaining five research-oriented pharmaceutical companies with headquarters in Germany, which sustainably invests in research and development (R&D). As percent of revenues, Grünenthal's R&D investments are significantly above industry average and amounted to about 25% of revenues in 2011. In contrast, the industry is reporting declining R&D expenditures. Grünenthal's research and development strategy concentrates on selected fields of therapy and state-of-the-art technologies. We are intensely focused on discovering new ways to treat pain better and more effectively, with fewer side-effects than current therapies and by improving the quality of life of those affected by pain. Our intensive search for innovative ways to relieve pain better distinguishes us from our peers.

Unique R&D Model

Our unique business model and innovation philosophy builds on filling our pipeline by internal research, licensing, and networking with academics and biotechs. In addition, R&D through to proof-of-concept is run as a stand-alone business to allow us to benefit from a combined scientific and entrepreneurial orientation. In our partnering model, we take the lead during early stages of research and in the first development phases. After proof-of-concept, we partner for late-stage development of our substances to share development expertise, risk, and costs, as well as future market potential. This enables us to dedicate disproportionately high levels of resources to early discovery and development. The proven success of our unique business model makes us confident that our commitment to innovation will ensure sustainable growth in the future.

Proven Track Record

Grünenthal's portfolio comprises a large number of highly effective treatment options for chronic as well as for acute pain conditions. Our products are available in more than 155 countries. One growth driver out of our innovative pipeline is INTAC®, an innovative formulation technology raising the hurdle against prescription drug abuse and protecting intended drug action. Another successful example of our partnering model is Tapentadol, which was discovered by Grünenthal and further developed and commercialized with our partner Johnson & Johnson. With Tapentadol, we developed a novel centrally acting analgesic that combines a μ-opioid-receptor agonist (MOR) and a noradrenaline-reuptake inhibitor (NRI) in one molecule. Tapentadol is the first representative of a proposed new pharmacological class called MOR-NRI and is effective against severe acute and chronic pain in adults, which can be adequately managed only with opioid analgesics. For more information, visit www.grunenthal.com.

Think Innovation. Feel Life.®

The Grünenthal Group is an independent, family-owned, international research-based pharmaceutical company headquartered in Aachen, Germany. Building on our unique position in pain treatment, we aspire to be the most patient-centric company and thus to be a leader in therapy innovation.

- Founded in 1946 in Stolberg, Germany
- Altogether, the Grünenthal Group has affiliates in 26 countries worldwide
- Today approx. 4,200 employees are working for the Grünenthal Group worldwide
- Our products are available in more than 155 countries
- In 2011, Grünenthal achieved revenues of € 947 mn.

www.grunenthal.com

GRÜNENTHAL

HOVIONE
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East Windsor, NJ 08520
T: (609) 918 2600 F: (609) 918 2615
E: hello@hovione.com
Website: www.hovione.com

The Comprehensive Solution Provider for the Pharmaceutical Industry

Hovione is a global company with over 50 years of experience in Active Pharmaceutical Ingredient (API) and Drug Product Intermediate development and compliant manufacture. With four FDA-inspected sites in the US, Ireland, Portugal, and China, the company focuses on the most demanding customers, in the most regulated markets.

Hovione offers technologies as well as integrated API solutions for all drug delivery systems, from oral to injectable and from inhalation to topical applications. Specializing in complex chemistry and particle engineering, Hovione undertakes all services related to the development and manufacture as well as formulation development and clinical supply of the final dosage form to Phase II. In the inhalation area, Hovione is the only independent company offering such a broad range of services.

Hovione has the capabilities to develop inhaled drug products from the ground up, starting at the API, with a development strategy that encompasses the molecule, the crystal, the powder, and the unit dose, as well as the delivery device. Only with integrated development, can we be sure of efficient delivery and a stable product.

From Proof of Concept Studies to Full Commercialization

Hovione is unique in providing optimization and scale up to full commercial support and eliminating the delays and costs of an intercompany transfer. Hovione's expert team of scientists and engineers provides a unique set of skills and experience along with an impeccable worldwide record of Quality. We operate using state-of-art methodologies: Quality by Design (QbD), Process Analytical Technologies (PAT), Process Modeling for optimization and scale up along with Lean Manufacturing are part of our DNA. Hovione has successfully taken projects through QbD filings to NDA approval and commercial launch.

Technologies

The company is one of the very few that offers a series of innovative particle engineering technologies to solve problems, such as poor bioavailability, patient acceptability, or enabling optimal delivery by non-oral routes of administration. These fall into three categories:

- Crystal design (eg, controlled crystallization, co-crystals)
- Particle size reduction (eg, jet milling, wet polishing, and nanoparticle generation)
- Amorphous solid dispersions (eg, spray drying, hot melt extrusion, spray congealing, inclusion complexes)

Hovione has further complemented these services with the formulation of dosage forms and clinical manufacture and is able to support highly potent compounds with many of these technologies.

The Company

Hovione has plants in Portugal, Ireland North America, Macau, China; R&D Centers in Portugal, North America, and China; and offices in Hong Kong, Switzerland, and India. Hovione employs 1,200 people worldwide and has more than 1300 m3 of flexible production capacity. Utilizing innovative technologies and methodologies, and with a global footprint, Hovione is an integrated solution provider to the pharmaceutical industry. Our aim is to do well what is difficult and to give our customers what they cannot find elsewhere.

Please visit **www.hovione.com**

Solubility Issues?

► Hovione dissolves them.

Most compounds in development face solubility challenges. Hovione's comprehensive approach provides multiple particle engineering technologies to address your specific development needs. Our experienced team of scientists and engineers applies state-of-the-art principles and tools to improve bioavailability. With a proven track record of commercialization, Hovione will drive your molecule from early clinical to market.

To learn more about how Hovione can overcome the solubility issues that stand in the way of your success, **visit hovione.com/pd or contact us at particledesign@hovione.com**

Rx360 Member

HOVIONE

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T: (800) 724-2372
Contact: Anthony Galasso (agalasso@lifesciencepr.net)
Website: www.lifesciencepr.net

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

Public Relations/Media Relations

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

Investor Relations

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

Social Media Development/Management

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

Multimedia/Interactive/Web Design

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

SEO/SEM

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

Advertising Design

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

Traditional/Online Media Planning & Placement

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

Tradeshow/Event Planning

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

Research & Focus Group Services for:

- Brand Development
- Client Perception

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

We'll get you there.

Smarter. Faster. Easier.

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

Get Noticed. Get Funded. Grow Faster.

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

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

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

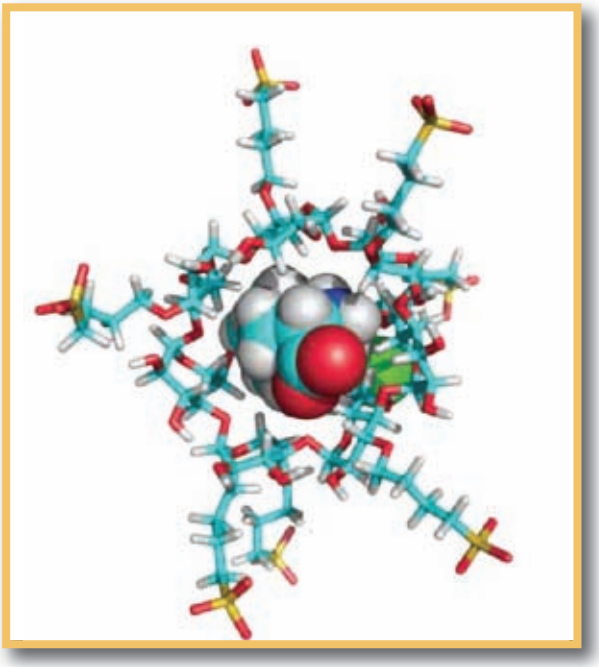
Call us at 800.724.2372 or visit lifesciencepr.net.

LifeSciencePR
we'll get you there.

Company Profile

CAPTISOL®
A Ligand TECHNOLOGY

Ligand Pharmaceuticals, Inc.
11119 North Torrey Pines Road, Suite 200
La Jolla, CA 92037
Toll Free: (877) 575-5593
E: orders@captisol.com
Website: www.captistol.com



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

Captisol® is a patent protected, uniquely modified cyclodextrin, whose chemical structure was rationally designed to maximize safety and optimize interaction to improve the solubility, stability, bioavailability, or lessen volatility, irritation, smell, or taste.

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

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 as well as realizing economies in staying with the same formulation throughout development. Deep industry experience with an extensive drug master file (DMF), technical expertise and worldwide collaborations make the Captisol®-enabling technology a solution to advancing a product toward commercialization.

For a complimentary 20-g sample, please visit www.captisol.com and click on "Try Captisol®" in the beaker.

MORE TECHNOLOGY.

MORE SOLUBILITY.

With many Cyclodextrins, you're only adding new issues into the equation. Not with Captisol. With revolutionary, proprietary technology, Captisol is rationally engineered to significantly improve solubility, stability, bioavailability and dosing of active pharmaceutical ingredients.

SOLVE PROBLEMS. WITH CAPTISOL SOLUTIONS.

CAPTISOL®

CAPTISOL.com

Company Profile

LYOPHILIZATION TECHNOLOGY, INC.
Integrating Science and Technology

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

Lyophilization Technology, Inc. (LTI)

is a Contract Development and Manufacturing Organization focused on all aspects of Lyophilization. A talented and dedicated staff, skilled through experience, is coupled with in-house capabilities in product development, process engineering, clinical manufacturing, and technical support. Recognized as an industry leader, the company has a proven reputation in providing innovative solutions, achieving desired results, and exceeding client expectations.

Major Products/Services

LTI has successfully developed formulations, manufacturing processes, and prepared material for clinical trials for over 384 diverse products. Gain the benefits of the experience and capabilities for creating solutions for the unique needs of lyophilized products.

- Anti-infectives
- Human/Recombinant Biologics
- Vaccines
- Oncolytics/HPCs
- Small Molecules/Therapeutics
- Diagnostics

Capabilities

- Preclinical to Phase II Clinical Materials, lyophilized and liquid products
- Dedicated/disposable product contact items/equipment
- Containment capabilities for handling cytotoxic/high potent APIs
- Lyophilizers ranging from 0.2 m^2 to 4.5 m^2
- Praxair ControLyo™, Nucleation On Demand *New*
- Vials from 2 to 160 mL and novel delivery systems
- Cartridges/syringes from 1 to 50 mL *New*
- Bulk Lyophilization or Drying
- Batch sizes to 75 L
- Drug and Device Registration/DEA license
- US/EU complaint

Development Sciences

Development services are conducted with a product quality and manufacturing mindset. This entails considering product administration, stability, and processing requirements from the start. Distinct development and process laboratories provide ample capacity for small-to-medium scale formulating through fill and finish activities. Filling, stoppering, and loading the qualified pilot-scale lyophilizers are completed in certified Class 100 clean rooms to emulate aseptic manufacturing conditions.

- Thermal Analysis
- Product Design
- Formulation Development
- Cycle Design/Refinement
- Product Characterization
- Toxicology Material

Clinical Manufacturing

The Clinical Manufacturing Area (CMA) is flexible for preparation of products with unique requirements, adheres to aggressive project timelines, and is fully cGMP compliant. The dedicated CMA includes separate controlled areas for warehousing, preparing materials, compounding, fill/finish, and inspection. The aseptic processing suite features containment and isolation technology. The operation has been inspected and approved for handling BSL-2 material.

- Preclinical
- Phase I
- Phase II
- Liquid Fills

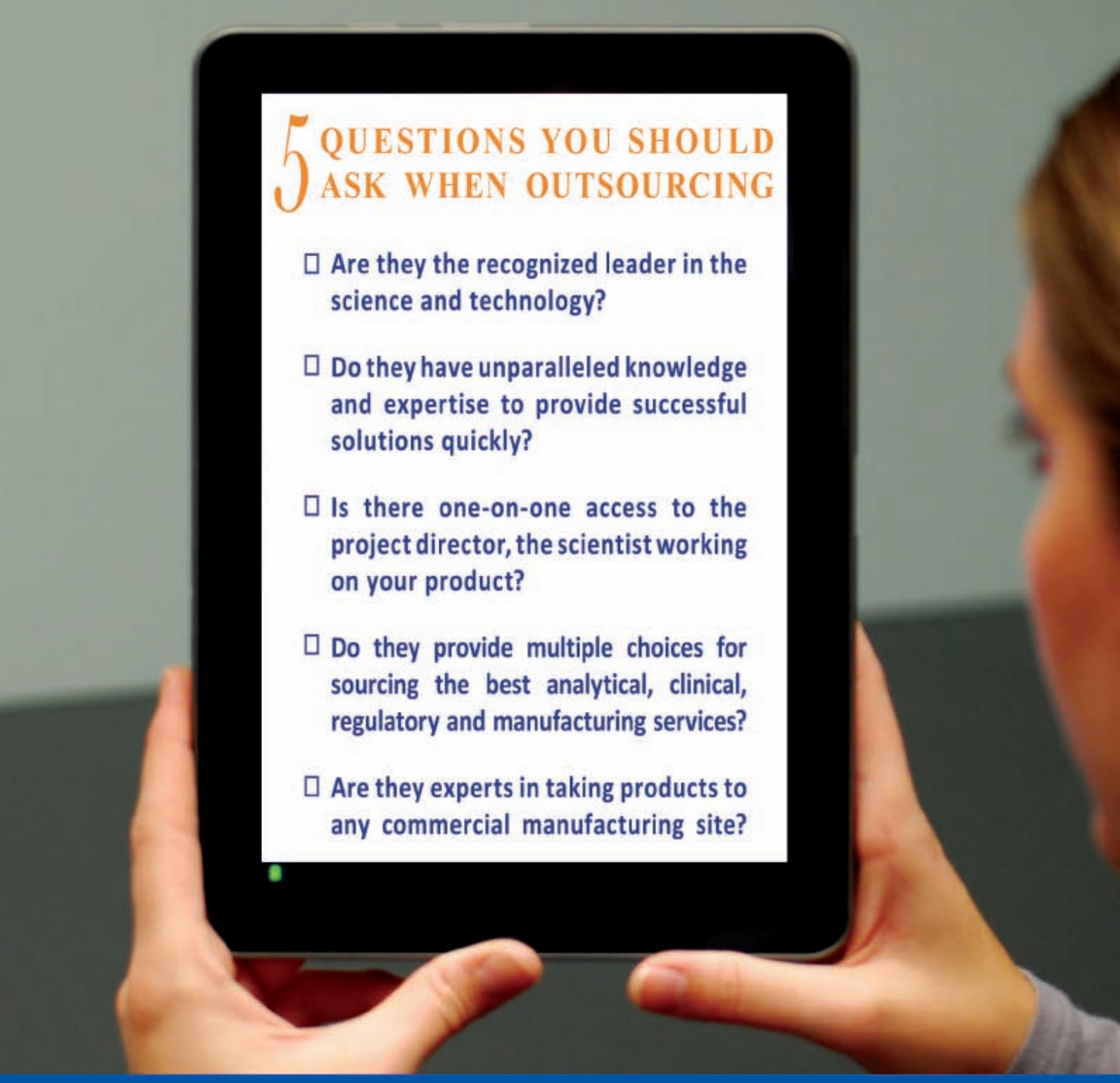
Technical Services

The broad range of experience in a wide variety of products provides a specialized expertise from which you can capitalize. Technical services are available providing support for all aspects of lyophilization.

- Customized Training
- Validation
- Investigations
- Quality/Compliance

Major Markets

LTI has provided lyophilization-focused Development and Clinical Trial Material Manufacturing services to more than 296 biotechnology and pharmaceutical clients spanning from virtual, small to large multi-national companies over 20 years.



Benefit from the focused expertise gained from working on 384* diverse products, collaborating with 296* companies over 20 years.

**As of September 2012*

Talk with the people who can provide you the right answers

Development Sciences Clinical Manufacturing Technical Services

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Integrating Science and Technology

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www.lyotechnology.com • inquiry@lyo-t.com

Unique Drug And Oxygen Delivery Systems

NOVALIQ

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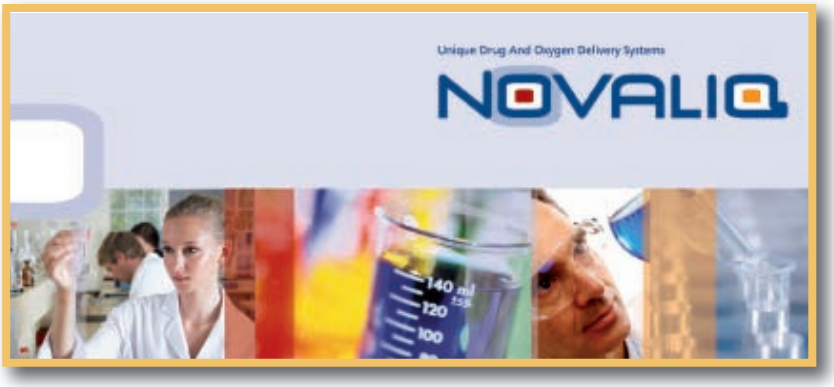

The Company

Novaliq GmbH, based in Heidelberg, Germany, is a drug delivery company developing non-aqueous formulations for poorly soluble drugs for ocular drug delivery.

The Technology

EyeSol™ is a novel topical ocular drug delivery system for poorly soluble drugs. The anterior part of the eye is amongst the most readily accessible organs of the body; however, drug delivery to eye tissue is particularly problematic. This is reflected by the notoriously poor bioavailability of topical ocular drug formulations of 5% or less. A standard water drop of around 40 to 50 µL will activate the blinking reflex, and most of the topically administered dose is washed away within 15 to 30 seconds after instillation.

To make matters even more complicated, meanwhile, up to 75% of NCEs are considered poorly soluble even for oral administration. In short, a drug is considered poorly soluble if the required dose cannot be dissolved in 250-mL aqueous medium. An aqueous eye drop has a volume of 40 to 50µL, 5000 times less volume. This exacerbates the solubility problem by several orders of magnitude.

Three major issues need to be addressed for ocular formulations - safety, bioavailability, and stability. These requirements are fulfilled by EyeSol™, Novaliq's proprietary ocular drug delivery technology. EyeSol™ is based on Semi−Fluorinated Alkanes (SFA). SFAs are a special class of fluorocarbon compounds that are used for more than 10 years in the posterior field in thousands of patients with an excellent safety profile. Their low viscosity and surface tension result in much smaller droplet sizes of around 15 µL, around three times less than a standard aqueous drop. Thus, spill over and the immediate losses of the majority of the administered dose are avoided with an obvious implication on the bioavailability. In addition, the refractive index of SFAs is similar to water so that vision is not impaired in contrast to emulsions and oily drops. Due to their amphiphilic nature, SFAs dissolve a number of therapeutically relevant poorly water-soluble compounds, such as Cyclosporine A and Tacrolimus. The aqueous-free environment increases stability by preventing oxidation and hydrolysis.

The Product

CyclASol™ is the first Cyclosporine A solution for dry eye disease. This proprietary product is based on the EyeSol™ technology. So it is provided preservative free in multi-dose units. The absence of surfactants, irritating preservatives, and the avoidance of blurry vision associated with emulsions leads to improved tolerability and convenience.

CYCLASOL™

PERC Pharmaceutical Education & Research Center

...supporting Pharma Analytical & Formulation Research

PHARMACEUTICAL EDUCATION & RESEARCH CENTER (PERC)
Campbell University College of Pharmacy & Health Sciences
PO Box 1090
Buies Creek, NC 27506

The Pharmaceutical Education & Research Center (PERC), a part of Campbell University's College of Pharmacy & Health Sciences, is a pharmaceutical contracting organization, which provides high quality analytical research, formulation development, small-scale production services, and analytical services for compounding pharmacies at competitive prices without the extensive overhead and bureaucracy of larger contract formulation development organizations.

The facility houses the Centers of Excellence for Analytical R&D and Formulation Development. PERC operates out of a 6,800 sq. ft. facility which contains the same technology and equipment currently utilized in the pharmaceutical industry along with dedicated personnel with extensive pharmaceutical industry experience (over 100 years).

The Center of Excellence for Analytical R&D provides a variety of analytical services including API Phys/Chem properties, deformulation, TM development, stability studies, particle sizing (nm to mm), Franz cell diffusion studies, residual solvents (GC). The Analytical center has numerous state-of-the-art instruments such as DSC, TGA, MSA, PXRD, particle size analyzers, HPLC, GC, LC/MS, UPLC/MS, and GC/MS, etc.

The Center of Excellence for Formulation Development has the experience, equipment, and resources to help clients with formulation development and small-scale production of all dosage forms. The Formulation center capabilities include tablet compression studies, encapsulation, fluid bed wet granulation, tablet and bead coating, lyophilization, sterilization cycle development, etc.

The Analytical services for Hospitals & Compounding Pharmacies include the identification of API, label strength assay, stability study evaluations, identification of API in finished products (including controlled substances).

Please contact us for your analytical and formulation research needs.

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QC/Analytical R&D Lab Manager
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pjohnson@campbell.edu

Scott Staton
Operations & Formulation Manager
(910) 814-4346
sstaton@campbell.edu

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COLLEGE OF PHARMACY & HEALTH SCIENCES

www.campbell.edu/PERC

PARTICLE SCIENCES
DRUG DEVELOPMENT SERVICES

PARTICLE SCIENCES, INC.
3894 Courtney Street, Suite 180
Bethlehem, PA 18017
T: (610) 861-4701
Website: www.particlesciences.com

For 21 years, Particle Sciences has been developing innovative drug products for our clients. Our international list of clients include venture backed start-ups, foundation and government funded organizations, and over half of the world's largest pharmaceutical and biotechnology companies. We specialize in formulating BCS II and biologics with a range of technologies including milling and nanoparticulate approaches, solid solutions, semisolids, and drug/device combination products, all aimed at optimizing the delivery of your API.

We are a full-service CRO providing complete formulation development, GMP/GLP analytic and bioanalytic methods development and testing, and clinical trial material manufacturing in our sterile, non-sterile, and high-containment clean rooms. We are DEA and FDA registered and work with highly potent compounds. At Particle Sciences, We Deliver®, taking your API from concept to clinic.

Our Approach

Drug delivery has advanced beyond dosage form specialization. Most APIs under development today have issues ranging from solubility to stability. Technologies that address these challenges cross dosage form boundaries. Particle Sciences is the leader in this API-centric trend. We believe a fundamental understanding of your compound and delivery goals is the key to success. At Particle Sciences, we use the most advance tools to ensure an efficient process, including DOSE®, our own solubility characterization paradigm, Design of Experiments, and state-of-the art equipment. Our clients' needs are thoroughly discussed and documented prior to initiating a project so that everything we do is on mission and makes the most of our clients' resources.

Technology

Our staff has extensive experience in drug delivery formats, including micro- and nanoparticulates, emulsions, suspensions, encapsulated APIs, and controlled-release dosage forms. Fine-particle and nanoscale systems have been a focus of Particle Sciences since its inception in 1991. We employ technologies ranging from milling to controlled precipitation to polymeric solid solutions. Particle Sciences has all the necessary instrumentation and in-house expertise to rapidly produce and characterize these systems. Additionally, we have the industry's leading dedicated drug/device combination-product team with full compounding, injection-molding, and analytic capabilities.

Client-Focused

Clients' projects receive individualized attention. Projects are overseen and coordinated by a dedicated project manager in conjunction with a cross-functional team that remains constant throughout the life of the project.

Integrated Process

Through a combination of preformulation, formulation, analytic, bioanalytic, and manufacturing services, Particle Sciences provides clients with a powerful and integrated solution to most efficiently take a drug from concept to clinic. With years of experience to draw upon, Particle Sciences can confidently handle difficult APIs, complicated intellectual property terrains, and challenging delivery goals to arrive at the simplest, most efficient solution to meet your needs.

THE DRUG DELIVERY EXPERTS

Particle Sciences is the leading BCS II formulation group. We have a fully integrated suite of services, including preformulation, formulation , analytic, bioanalytic, and clinical trial manufacturing. We work with highly potent compounds, controlled substances, and can produce both sterile and non-sterile drug products. In addition to standard technologies, Particle Sciences is a global leader in drug/device combinations, milled nano-particles, and lipidic delivery systems. For more information, please visit **www.particlesciences.com**, email **info@particlesciences.com**, or call us at **(610) 861-4701**.

AN INTERNATIONALLY RECOGNIZED LEADER

PARTICLE SCIENCES
DRUG DEVELOPMENT SERVICES

3894 Courtney Street | Bethlehem, Pennsylvania 18017
610·861·4701 ph | 610·861·4702 fax www.particlesciences.com

Company Profile

PharmaCircle LLC
Encinitas, CA 92024
T: (760) 436-1199 E: contact@pharmacircle.com
Website: www.pharmacircle.com

PharmaCircle™ is a knowledge management company providing pharmaceutical, biotechnology, specialty pharma, drug delivery, generic, and pharmaceutical service companies with comprehensive online product, technology, and business-related information and analysis.

PharmaCircle provides critical data and analysis on all aspects of the pharmaceutical business with global coverage of research, development, regulatory, clinical, and business activities. Our clients include almost all of the top 20 pharmaceutical companies as well as numerous commercial and emerging-stage biopharmaceutical companies and suppliers. We work closely with the scientist, business, clinical, and regulatory folks as well as information/CI specialists to provide answers to challenging questions related to their business needs.

What makes PharmaCircle different?

A combination of unique data and analysis along with proprietary know-how in search and display technologies helps make PharmaCircle much more than a database.

- PharmaCircle's management team brings you more than 25 years of first-hand experience in the field.
- No other service can match PharmaCircle's content in the areas of drug delivery, formulation, excipients, delivery device, and other important product/pipeline details and information.
- PharmaCircle provides you with the tools to search hundreds of important company, product, and technology attributes and display them dynamically in tables or charts to help you make important product, technology, and service decisions.
- PharmaCircle's customer support, provided by its top management, is unmatched in the business.

PharmaCircle coverage includes:

R&D	Regulatory	Business	Other
Products/Pipeline	Products/Pipeline	Products/Pipeline	Veterinary Products
Product (FDA)	Product (FDA)	Deals / Acquisitions	Vaccines
Discovery Technology	EU Label (Eudrapharma)	Venture Capital	Combination Products
Formulation/DD Technology	US Label (FDA)	Companies	
Excipients (FDA)	Japan Label (PMDA)	R&D Cost	
Molecule Info	Canada Label (HPB)	News/History	
DD Patents	Approval Package (FDA)	Product Sales	
Clinical Trials (FDA)	Adverse Events (FDA)	Lifecycle Studies	
Clinical Trials (EU)	Packaging Info (FDA)	Packaging Info (FDA)	
Dissolution Methods	Paragraph IV (FDA)	Supply Chain	
DD Technology Reviews	Drug Master Files (FDA)		
DD Technology Tables	Orange Book (FDA)		

Much More than a Database!

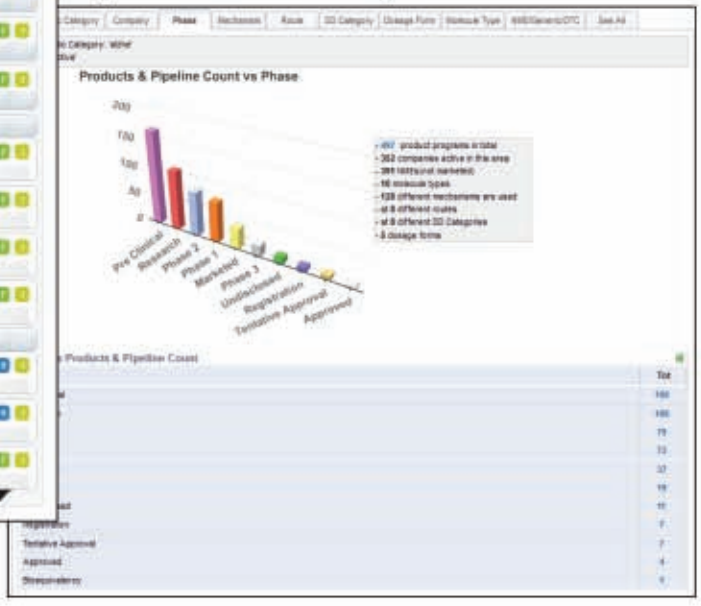
With an intuitive interface PharmaCircle™ provides pharmaceutical professionals with the tools to find, analyze and drill down on information that can uncover new opportunities.

PharmaCircle™ provides you with vital product, business and industry information. Providing more than 60 separate search modules covering the pharmaceutical research, development, regulatory and business sectors with three separate search interfaces, PharmaCircle provides you with the resources to understand and make better decisions.

Online. Quickly. Intuitively.

Simpler Search Interface

Dynamic Interactive Output



PHARMACIRCLE™

For more information or a demo:
T: 760.436.1199, contact@pharmacircle.com
www.pharmacircle.com

Company Profile

ResearchDx
5 Mason
Irvine, CA 92618
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Website: www.researchdx.com

ResearchDx is the leading Contract Diagnostics Organization (CDO) for the biopharmaceutical and diagnostic industries. We provide integrated, turnkey, flexible services that are focused on our customers' objectives. We manage the entire diagnostic development process - from initial assay concept and discovery through clinical research to regulatory approval. At ResearchDx, we take contract R&D for diagnostics to the next generation.

The founders of ResearchDx have a passion for the advancement of personalized medicine. In founding the first-ever CDO, they help biopharmaceutical companies overcome the barriers to developing diagnostic products. ResearchDx has extensive experience in genetics, clinical research, and clinical laboratory services.

Experience You Can Trust

The ResearchDx management team has unparalleled experience in managing clinical laboratories, designing and managing clinical research, and navigating the complex regulatory environment specific to diagnostics.

Integrated Services

Trust ResearchDx to provide independent and unbiased guidance, expert analysis, and seamless integration of all the services you need to develop a diagnostic product - including assay development, clinical laboratory services, clinical trial design and conduct, project management, manufacturing, regulatory guidance and submissions, and consulting. In the era of personalized medicine, ResearchDx is forging a new path as the first-ever CDO. Biopharmaceutical companies need diagnostics partners that can easily and readily adjust to meet new or unexpected challenges during the development process. The traditional Contract Research Organization (CRO) simply cannot meet all the demands of developing companion diagnostics. As a CDO, ResearchDx offers integrated, flexible services that you can trust to stay on track.

Flexibility

ResearchDx can adapt to meet your complex and constantly evolving needs for diagnostic development. We can build, validate, and perform any assay that your business demands, or alternatively work with competing technology vendors to ensure the best fit for your application.

Focus On Your Business

Your diagnostic development is ResearchDx's sole focus. You can rest assured that we have the experience and dedication to ensure the fastest possible path to commercialization for your diagnostic product needs.

Providing our partners the fastest path to market.

A Contract Diagnostics Organization (CDO) is your complete partner for diagnostics development.

We can manage all or any part of development from initial assay discovery through clinical research to regulatory approval. Our services include research project design, conduct, and FDA submission; laboratory assay development, validation, and sample testing in our CAP/CLIA lab; cGMP assay and reagent manufacturing; and expert guidance across the entire process.

"Our partnerships are based on flexibility, allowing us to either build and validate any assay without bias towards existing product platforms, or to work with emerging technology to ensure the best solution."

Mathew W. Moore *PhD, Principal, ResearchDx*

To learn more about how ResearchDx can help you, contact us at:
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or call **866-225-9195**

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Call For Papers

Contributed Papers Submission Deadline:

February 13, 2013

SUBMISSION DETAILS:
www.aaps.org/nationalbiotech

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American Association of Pharmaceutical Scientists

Company Profile

Tapemark
1685 Marthaler Lane
West St. Paul, MN 55118
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E: tmsales@tapemark.com
Website: www.tapemark.com

Tapemark is a CDMO (Contract Development & Manufacturing Organization) providing web-based (flexible roll goods) manufacturing for Drug, Device, and Combination Products. Supported single-use drug delivery formats include:

- Active and passive transdermal patches
- Oral and transmucosal soluble film
- Topical patches and pads
- Tapemark's patented Snap!® and Snapplicator™ unit-dose packaging for semi-solids

Tapemark is a market leader in transdermal drug delivery formats, both active and passive delivery systems. Transdermal patches support controlled permeation of a drug through the skin, either independently or in combination with enhancer technologies, including iontophoresis, microneedles, thermal poration, and dermabrasion. Tapemark has worked with multiple transdermal products including matrix, reservoir and hydrogel-based designs supporting a range of bulk drug viscosities, and is experienced in placement of traditional button batteries or printed electronic batteries.

SoluStrip™ is a soluble film strip in a unit-dose pouch containing your API (active pharmaceutical ingredient), individually packaged for maximum protection. SoluStrip is ideal for oral and transmucosal (buccal, sublingual) delivery of Rx and OTC drugs, including Scheduled Drugs. SoluStrip supports optimal drug efficacy and dosing safety. Convenient and portable, SoluStrip is waterless - requiring no glass of water to administer the drug, thus enhancing compliance.

For topical treatments, Snap!® or Snapplicator™ dispenses a precisely measured single dose of your Rx or OTC cream, gel, ointment, or lotion. Tapemark's unique, patent-protected packaging is available in sizes to meet fill volumes of less than 0.5 ml to over 15 ml. Snap! delivers a pre-measured dose in an easy-to-use disposable package that opens with one hand, offering portability, safety, and convenience. Snapplicator adds an applicator for "no touch" convenience; keeping hands clean leads to better compliance and therefore efficacy. As the Snapplicator is opened, the contents are dispensed right through the applicator.

Tapemark's core competencies include disciplined, data-driven process development, with full understanding of statistical analysis and successful project management tools, including a phase-gate approach to development; Lean Manufacturing, Six Sigma, and Continuous Improvement to support your product effectively throughout its lifecycle; and the company's proven FDA-registered Quality System:

- FDA registered as a Drug, Device, Food, Cosmetics, and Dietary Supplements contract manufacturer
- cGMP-compliant
- ISO 9001 and ISO 13485
- CE Mark certification
- DEA registered as a Schedule III-V Manufacturer of Controlled Substances
- Successfully audited by the European Union, Japan, Australia, and Korea

From clinicals to commercial, Tapemark is your CDMO partner of choice, scaling production services for your clinical trial volumes through projections for launch and commercial production.

Company Profile

UPM Pharmaceuticals®, Inc.
6200 Seaforth St.
Baltimore, MD 21224
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Website: www.upm-inc.com

UPM Pharmaceuticals®, Inc. is a Baltimore-based drug development and contract manufacturing company providing customized formulation development, manufacturing, and analytical services to pharmaceutical, biotechnology, and university clients. Fully appreciating that flexibility and time-to-market are critical; UPM is highly responsive to clients' program changes and specializes in developing creative solutions to unique challenges. UPM is characterized by the timeliness and thoroughness with which all projects are managed. Every step of the way, UPM Pharmaceuticals works to advance and optimize products through up-to-date resourceful approaches, while adhering to the highest quality standards. Through the years, our staff and systems have been consistently challenged by FDA, DEA, QP, and client audits, and we have passed these rigorous inspections repeatedly.

Scientific Expertise – Access to some of the industry's best formulation design specialists, manufacturing specialists, and analytical chemists, who are known for developing innovative solutions to difficult development challenges.

Rapid & Responsive Turnaround – Our scientists and senior managers utilize daily planning meetings and a master scheduling process that provides for timely and responsive project management.

Quality Assurance & Document Control – Our highly experienced quality assurance personnel implement complete cGMP quality and regulatory systems that support formulation development, clinical batch manufacturing, and analytical work-up.

Capital Investment – Recent equipment acquisitions have increased our capabilities for solid dose formulation development, including mini-scale R&D proof-of-concept manufacturing (BREVI-BATCH™), low solubility compound processing, uHPLC sample analysis, and bi-layer tableting.

Manufacturing Facilities – Additional expansion of the manufacturing facility, including a low-humidity/high-potency suite, direct API filling suites, and an expanded packaging line suite will allow UPM to continue to meet our clients' increased manufacturing demands.

Services Offered

- BREVI-BATCH™ mini-batch proof-of-concept studies
- Formulation Development
- Low Solubility Processing
- Wet Granulation
- Dry Granulation/Roller Compaction
- Particle Size Analysis
- Tableting
- Bi-layer Tableting
- Tablet & Particle Coating
- Direct API fill Into capsules for proof-of-concept studies
- Capsule Filling
- Feasibility to Small-Scale Commercial
- cGMP Manufacturing
- CTM Packaging
- Stability Testing
- Blinding of Clinical supplies
- Analytical Services

UPM Pharmaceuticals®
Formulating Your Future™

UPM's Flexibility. Your Success.

UPM Pharmaceuticals has the flexibility to consistently meet your solid dose needs. We are a partner committed to optimizing your process and combining expertise to ensure you meet strategic and time-sensitive goals.

FORMULATION DEVELOPMENT
CLINICAL MATERIALS SUPPLY
ANALYTICAL SERVICES
COMMERCIAL MANUFACTURING
COMPLEX FORMULATIONS

To learn more, visit **www.upm-inc.com**
or call **+1 410 843 3738**.

COMPANY PROFILE

XCELIENCE
5415 West Laurel Street
Tampa, FL 33607
Corporate Phone: (813) 286-0404 Business Development Phone: (608) 643-4444
F: (813) 286-1105 E: Info@xcelience.com
Website: www.xcelience.com
Contact: Randall Guthrie, Vice President

Xcelience is a premier provider of formulation development and manufacturing solutions with a solid reputation for accelerating early phase development. Our outstanding quality record, drug development expertise, disciplined project management, and willingness to customize enables us to deliver real advantage to pharmaceutical innovators focused on small molecule development. Partnering with a specialist like Xcelience for early phase development can reduce product risk and accelerate development timelines. Since 1997, Xcelience has been renowned for reliably expediting drug development and reducing compound risk. Our scientists have considerable experience overcoming challenging physical and chemical properties in a manner that results in improved solubility and compound bioavailability.

XCELIENCE ADVANTAGE

- Three-phase facility expansion increases capacity and processing speed for formulation development, analytical, GMP manufacturing, and packaging.
- Expanded clinical trial supplies manufacturing capabilities increase overall capacity, improve production times, and expand upon existing capabilities for production, coating, and encapsulation.
- New fully automated packaging line for primary bottling of tablets and capsules enhances the speed for batch packaging, shortens timelines, and enables packaging of larger batches.
- Global access to four Xcelodose® precision powder microdosing systems, which enable clients to fill very small amounts of powder into capsule speeding time to first-in-human studies.
- Liquid-in-capsule services for overcoming the challenge of poor aqueous solubility and improving compound bioavailability.
- Small-scale batch production for companies facing the challenge of limited API.
- Comparator product blinding.

SERVICES & CAPABILITIES

Preformulation
- Salt Screens
- Polymorph Screens
- Drug Substance Characterization
- Excipient Compatibility
- Accelerated Stability
- Chiral Stability

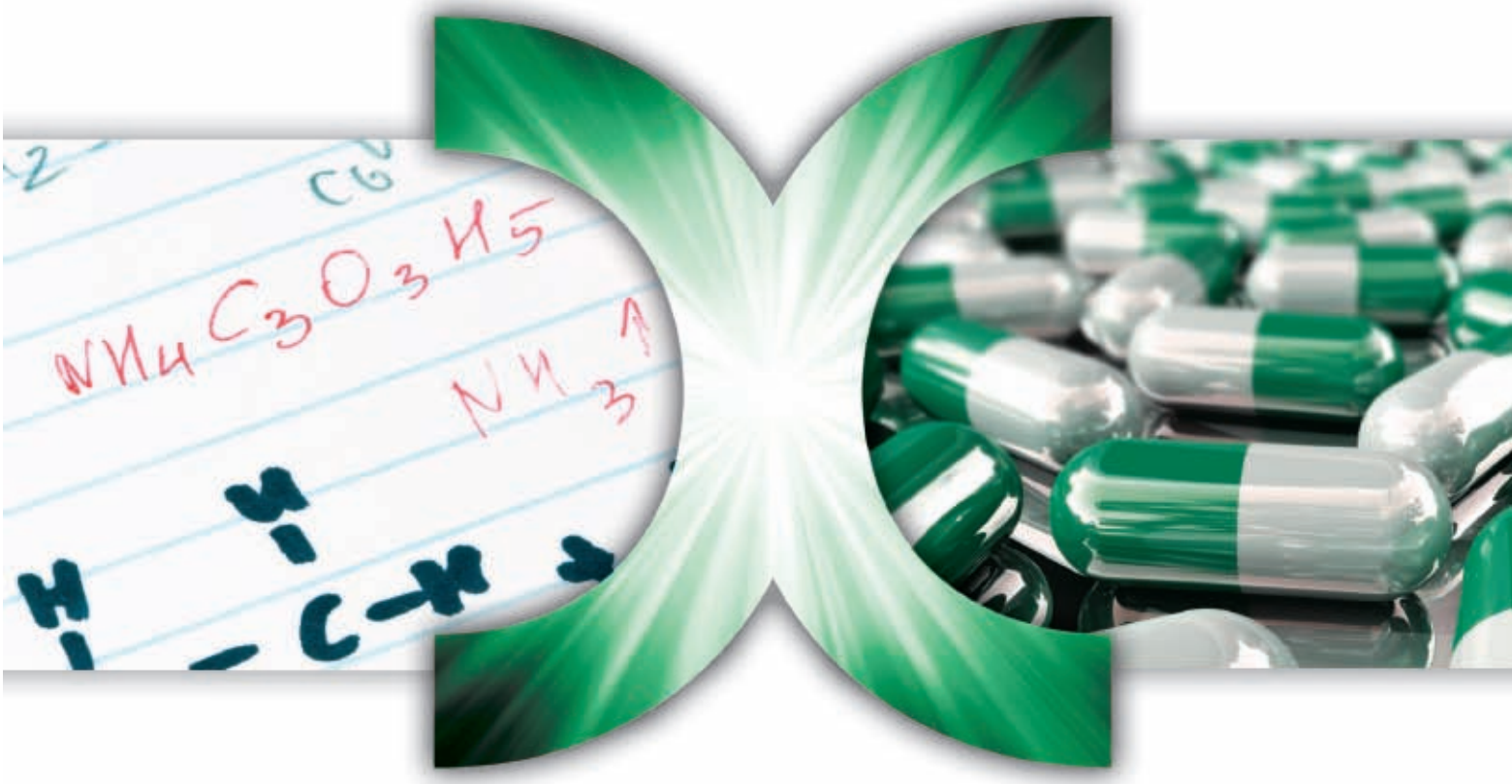
Analytical Services
- Method Development
- Qualification & Validation
- Raw Material Testing
- Stability Sample Analysis
- Dissolution Testing
- Residual Solvent Analysis
- Chiral Determination
- Cleaning Evaluations
- Technical Packages for Drug Substances

Formulation Development
- Solids (tablets, gelatin or HPMC capsules, sustained release, and coatings)
- Semi-Solids (ointments, creams, and gels)
- Dispersed systems (emulsions, suspensions)
- Liquids (orals, ophthalmics, parenterals)

Clinical Trial Supplies Manufacturing & Packaging
- API or Powder Into Bottle
- Powder Into Capsule
- Tablets & Capsules
- Liquid in Capsule
- Semi-Solids
- Non-Sterile Liquids
- Reference Product Blinding
- Matching Placebo Formulation
- Blinded Reference Product
- Process Qualification, Definition, Optimization & Transfer
- Clinical Packaging & Labeling

Stability Program Management
- ICH Conditions
- Protocol Design
- Report Generation
- Sample Analysis
- Secure Storage Area
- SLIM (our stability laboratory information management system, meets FDA standards for 21CFR11 compliance)

FACILITIES
Xcelience operates out of a cGMP-compliant, DEA-licensed facility located in Tampa, Florida, one of the most desirable cities in the world.



AT LAST

Early drug development made easy.

Xcelience® is your premier source for formulation development and clinical supplies manufacturing and packaging solutions.

Since 1997, Xcelience has been renowned for reliably expediting drug product development and clinical manufacturing for oral solid, semi-solid and liquid dosage forms. Our formulation development scientists have considerable experience overcoming challenges associated with physical and chemical properties of drug substance, or limited quantities of active pharmaceutical ingredient, in a manner that results in compounds with improved solubility and bioavailability.

Services include preformulation, analytical method development/validation, formulation development, clinical supplies manufacturing, and clinical packaging.

Partnering with a specialist like Xcelience for early phase oral dosage form development can accelerate drug development timelines and reduce risk. To learn more, visit www.xcelience.com, or call 1-608-643-4444.

Xcelience® Formulation Development

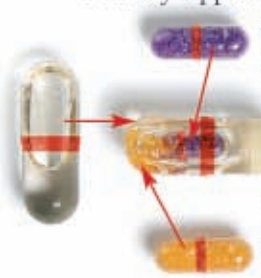
www.xcelience.com

Contact us today at **1.608.643.4444** or **info@xcelience.com**

THE ADVANTAGES

OF MULTI-PHASE, MULTI-COMPARTMENT CAPSULES ARE CLEAR

INNERCAP® Technologies Granted US Patent No. 7,670,612 on multi-phase, multi-compartment capsular delivery apparatus and methods for using the same.



March 23, 2010, Saint Petersburg, Florida USA, INNERCAP Technologies, Inc., an international drug delivery and specialty pharmaceutical company, recently announced the grant of US Patent No. 7,670,612 entitled "Multi-Phase, Multi-Compartment Capsular Delivery Apparatus and Methods for Using Same." The delivery system has uses for bio-pharmaceutical, pharmaceutical, medical foods and nutraceutical products. In addition to the existing New Zealand patent, this patent covers the company's multiphase multi-compartment delivery system used to enable the development of multicompartment, multi-phase delivery forms (two piece capsule based) of combination products that have compatibility, formulation or targeted delivery obstacles.

"This is a significant development for INNERCAP Technologies NOVACAP technology," said Fred H. Miller, Chief Executive Officer at INNERCAP. "The continued growth of our patent portfolio establishes INNERCAP as one of the leading companies in this space."

The delivery system and combinations covered by the patent have the ability to deliver therapeutic entities that have never been combined previously and now can be administered together, via an oral, implanted, or suppository capsule, in the most advantageous pharmacokinetic profile, utilizing different physical phases. This technology can therefore be used to enable capsule administration of compounds that are not normally administered as a combination product. The efficacy, safety, and side-effect profiles of drugs can be substantially improved using this delivery technology. It will also provide very significant quality-of-life improvements for patients and substantial economic savings for hard-pressed healthcare systems.

"INNERCAP's multi-phase, multi-compartment technology has been commercially manufactured and validated in several products, demonstrating that INNERCAP's delivery system creates real value to consumers and branded manufacturers," added Mr. Miller.

INNERCAP was represented by Cliff Davidson, Esq. of the patent firm Davidson, Davidson & Kappel, LLC (www.ddkpatent.com) based in New York City.

For more information contact us at the telephone number and email address below:

INNERCAP® TECHNOLOGIES, INC

United States Patent No. 7,670,612
US and International Patents Pending

9216 Palm River Road, Suite 203 • Tampa, FL 33619 USA • (813) 837-0796 • www.innercap.com • busdevelopment@innercap.com

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November/December 2012

Advertiser Index

STATEMENT OF OWNERSHIP, MANAGEMENT, AND CIRCULATION

1. Publication title: Drug Development & Delivery
2. Publication number: 1537-2898 3. Filing Date: October 30, 2012 4. Issue frequency: Monthly with combined Jan/Feb, July/Aug and Nov/Dec 5. Number of issues published annually: 9 6. Annual Subscription price: N/A 7. Complete mailing address of known office of publication: 219 Changebridge Rd. Montville, NJ 07045-9998 8. Complete mailing address of headquarters or general business office of publisher: 219 Changebridge Rd. Montville, NJ 07045-9998 9. Full names and complete mailing address of Publisher, Editor and Managing Editor: Ralph Vitaro - 219 Changebridge Rd. Montville, NJ 07045-9998, Dan Marino - 219 Changebridge Rd. Montville, NJ 07045-9998,10. Owner: Drug Delivery Technology, LLC - 219 Changebridge Rd. Montville, NJ 07045-9998 11. Known bondholders, mortgages and other security holders: None 12. N/A 13. Publication: Drug Development & Delivery 14. Issue date for circulation data: October 1, 2011 15. Extent and Nature:

	Average No. Copies Each Issue During Preceding 12 Months	No. Copies of Single Issue Published Nearest to Filing Date
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f. Total Distribution	16,847	16,669
g. copies not distributed	64	31
h. Total	16,911	16,700
i. Percent paid and/or requested circulation	97.3%	97.4%

16. Publication of Statement of Ownership for a requester publication is printed in the November/December 2012 issue

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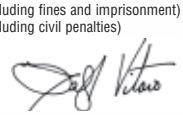

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Aptalis Pharmaceutical Technologies	51	908-927-9600	www.AptalisPharmaTech.com
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Drug Delivery Partnerships	66,67		www.drugdeliverypartnerships.com
Drug Development & Delivery	4,	973-299-1200	www.drug-dev.com
EAG Life Sciences	63	800-659-6059	www.eaglelabs.com/ls
ExcipientFest Americas	21	787-714-3000	www.excipientfest.com
Frost & Sullivan	68,69	201-477-8481	www.frost.com
Foster Delivery Science	3,64,65	860-630-4525	www.deliveryscience.com
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Novozymes	17		www.stabilizeyourformulation.com
Novaliq GmbH	9,82	+49 6221 50259 0	www.novaliq.de
Particle Sciences	84,85,Insert	610-861-4701	www.particlesciences.com
PERC	8,83	910-814-4346	www.campbell.edu/PERC
PharmaCircle	86,87	760-436-1199	www.Pharmacircle.com
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RDD Europe	62		www.rddonline/rddeurope2013
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UPM Pharmaceuticals	92,93	410-843-3738	www.upm-inc.com
Xcelience	94,95	608-643-4444	www.xcelience.com

If you want to rest easy, it pays to partner with the right CMO.

The journey to commercial drug supply can be a real nightmare — unless you choose the right CMO partner. When you choose JHP Pharmaceuticals, you can count on a team of specialists who have spent years developing the systems, expertise and invaluable insight necessary to help you steer clear of potential problems that can keep you up at night. We've helped some of the biggest names in the drug and biotech world bring sterile injectable products to market quickly and efficiently.

From the first clinical supplies to final production of large commercial batches, our expert account team will be right by your side. In addition, our manufacturing facility is fully cGMP compliant and offers the ultimate flexibility should you need to scale up at a moment's notice to meet unexpected demand.

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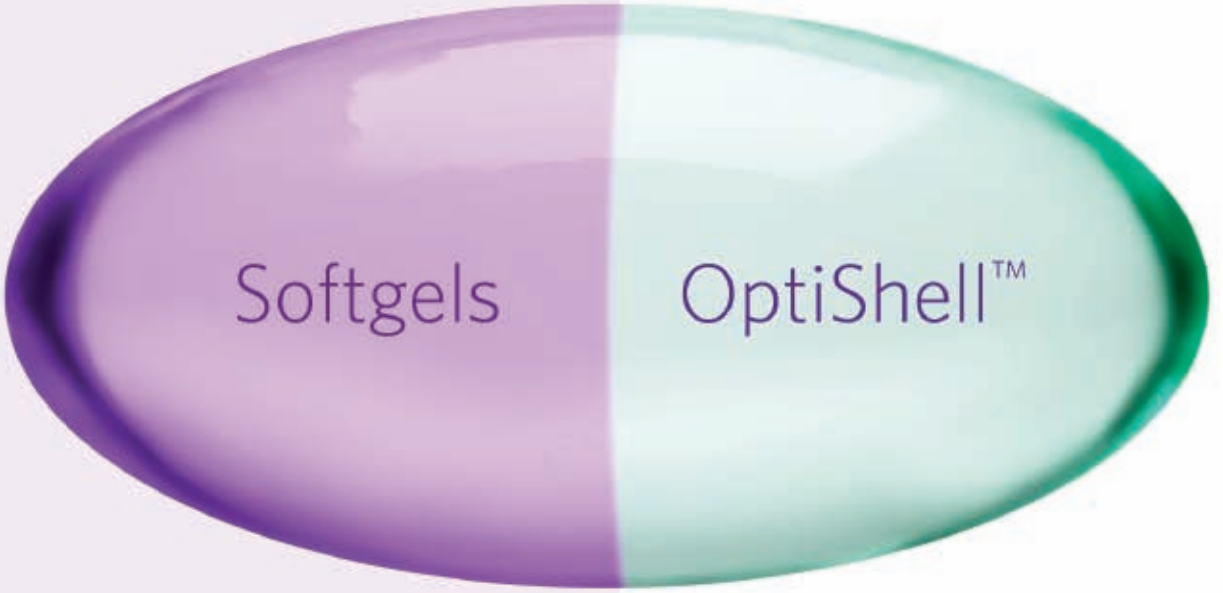
rp scherer softgel

New OptiShell™ capsules.

The optimal delivery technology for challenging compounds.
Our patented shell composition can handle semi-solid fill formulations to help you bring more products to market, faster.



Shell Composition	**Gelatin**	**Carrageenan** and modified starch
Fill Temperatures	**Lower** (up to 40°C)	**Higher** (up to 70°C)
Fill Formulations	**Solutions** and **suspensions**	**Semi-solid** and **highly-viscous** fills
Excipients Range	**Wide**	**Wider**
pH Levels	Slightly acidic to **neutral**	Slightly acidic to **alkaline**

DEVELOPMENT DELIVERY SUPPLY

Every molecule has a challenge. We have a soft capsule solution.
Call: + 1 888 SOLUTION (765 8846) Email: solutions@catalent.com Visit: www.catalent.com