Drug Delivery Technology®

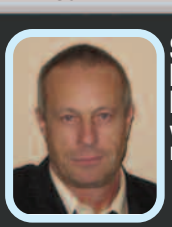
April 2008 Vol 8 No 4 www.drugdeliverytech.com

Investing in Combination Products

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

Bhupendra Prajapati, MPharm
The Upcoming Era of Nanomedicine: A Briefing

Christine M. Ford, MBA
Investment Trends Driving Combination Product Development



Stuart Madden, PhD
Which Way to Drug Approval?

IN THIS ISSUE

INTERVIEW WITH PHARMAFORM'S VP, BUSINESS DEVELOPMENT

MICHAEL CROWLEY, PhD

FEATURING

SPECIALTY PHARMA
Strategies For Business Development

Create your own formulation masterpiece with SPI Technologies

SPI Pharma™

Rockwood Office Park
503 Carr Rd, Suite 210
Wilmington, DE 19809
Tel. 800-789-9755

www.spipharma.com

THE ADVANTAGES

OF MULTI-PHASE, MULTI-COMPARTMENT CAPSULES ARE CLEAR

Deliver Incompatible Compounds
Deliver incompatible compounds in a single dosage form with different release profiles.

Multiple Release Profiles
Incorporate one or more release profiles into a single dosage form such as immediate, enteric, targeted, chronotherapy and pulsatile.

Higher Perceived Value
Consumers view multi-phase, multi-compartment capsules as having a higher perceived value than ordinary tablets, capsules and soft gels.

Choice of HPMC or Gelatin Capsules
With multi-phase, multi-compartment capsules you are not limited to just gelatin (animal-based product) but have the option of natural HPMC (hydroxypropyl methyl- cellulose) and alternative capsule materials.

Better Visual Appeal
Multi-phase, multi-compartment capsules have none of the dust and residue associated with powder capsules. Better visual product appearance translates to higher perceived value.

Increased Absorption and Bioavailability
Liquids naturally offer faster and increased absorption and availability of active ingredients.

Increased Profit Potential
Add up all the advantages. Expect higher sales…and high margins!

Multi-Phase System
Compounds can be delivered with the most advantageous pharmacokinetic profile such as liquids and solids

Faster Development
Multi-phase, multi-compartment capsules reduce the development time compared to bi-layer tablets to get a new product into clinical trials faster.

Smaller Capsules
Hard-shell capsules have thinner wall construction, allowing them to contain more ingredient in a smaller capsule versus thicker-shelled soft gel capsules. Hard shells have faster and more complete dissolution than soft gels.

Less Odor and Less Irritation
Reduces unpleasant ingredient taste and odor commonly found with tablets and traditional capsules. And, liquids provide less irritation than traditional delivery methods.

Tamper Proof Sealing
Band sealing reduces tampering and provides a non-permeable barrier to retard oxidation and increase shelf-life.

Unique Appearance
This new delivery system stands apart from look-alike products that crowd retail shelves.

Compounds
Deliver Pharmaceutical, bio-pharmaceutical and nutraceuticals in a single dosage form.

InnerCap™ Technologies, Inc

Patent Pending US-2005-0008690-A1

9745 International Court • St. Petersburg, FL 33716 USA • (813) 837-0796 • www.innercap.com • fmiller@innercap.com

Drug Delivery Technology

April 2008 Vol 8 No 4

PUBLISHER/PRESIDENT
Ralph Vitaro

EXECUTIVE EDITORIAL DIRECTOR
Dan Marino, MSc
dmarino@drugdeliverytech.com

CREATIVE DIRECTOR
Shalamar Q. Eagel

CONTROLLER
Debbie Carrillo

CONTRIBUTING EDITORS
Cindy H. Dubin
Debra Bingham
Jason McKinnie
Malcolm A. Teasdale

TECHNICAL OPERATIONS
Mark Newland

EDITORIAL SUPPORT
Nicholas D. Vitaro

ADMINISTRATIVE SUPPORT
Kathleen Kenny

Corporate/Editorial Office
219 Changebridge Road, Montville, NJ 07045
Tel: (973)299-1200
Fax: (973) 299-7937
www.drugdeliverytech.com

Advertising Sales Offices

East & Midwest
Victoria Geis - Account Executive
Cheryl S. Stratos - Account Executive
103 Oronoco Street, Suite 200
Alexandria, VA 22314
Tel: (703) 212-7735
Fax: (703) 548-3733
E-mail: vgeis@drugdeliverytech.com
E-mail: cstratos@drugdeliverytech.com

West Coast
Warren De Graff
Western Regional Manager
818 5th Avenue, Suite 301
San Rafael, CA 94901
Tel: (415) 721-0644
Fax: (415) 721-0665
E-mail: wjdegraff@drugdeliverytech.com

International
Ralph Vitaro
219 Changebridge Road
Montville, NJ 07045
Tel: (973) 299-1200
Fax: (973) 299-7937
E-mail: rvitaro@drugdeliverytech.com

Mailing List Rental
Candy Brecht
Tel: (703) 706-0383
Fax: (703) 549-6057
E-mail: cbrecht@mgilists.com

3M Drug Delivery Systems
INHALATION SYSTEMS

We're in the "competitive advantage" business.

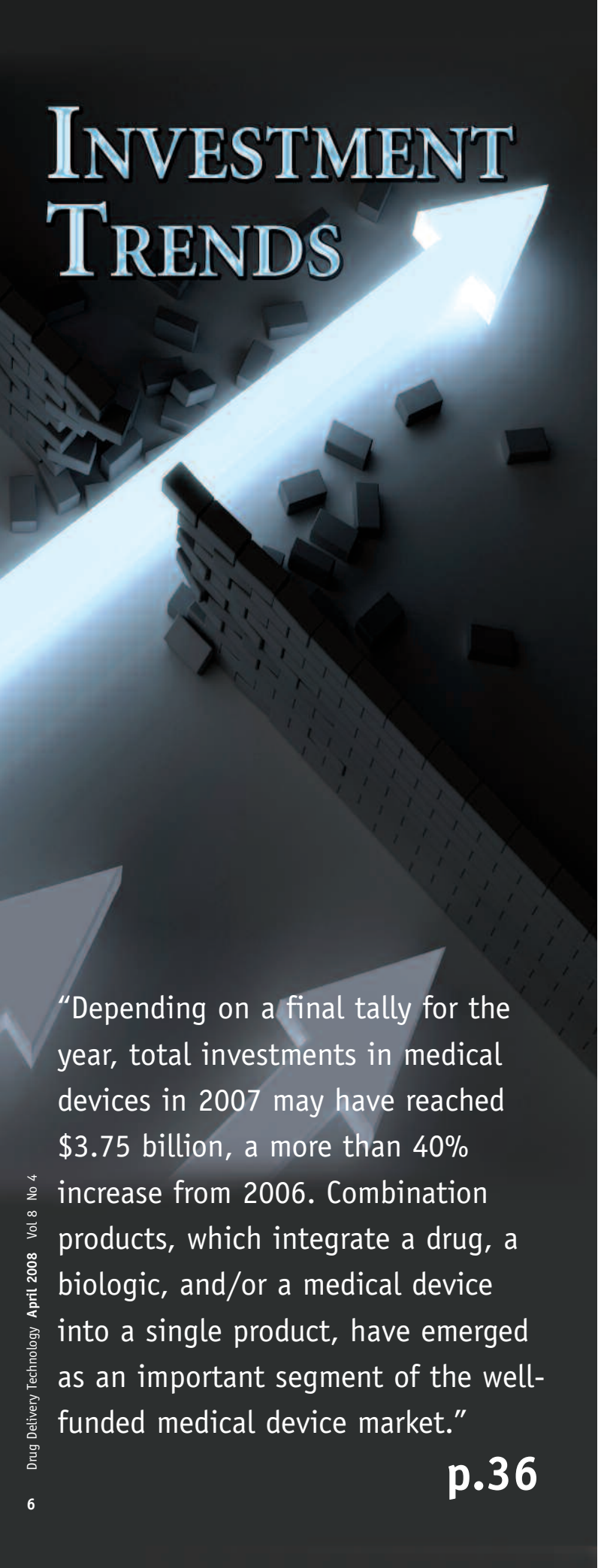
The inhalation expertise, efficiency and flexibility you need to reach your goals.

At 3M, we understand inhalation drug delivery. After all, we invented the metered-dose inhaler. In the 50 years since, we've learned that you need more than just a great inhalation device to gain an advantage. You need a flexible, expert partner. One who can create a customized solution for your formulation, meet worldwide production needs, and help guide you through regulatory approval. Our proven track record of global product development and regulatory approval combined with our efficient manufacturing processes help you succeed in a competitive marketplace.

For further information contact: US: 1 800 643 8086 ext 710
UK: 44 (0) 1509 613626
www.3M.com/ddsadv

ENABLING YOUR SUCCESS.

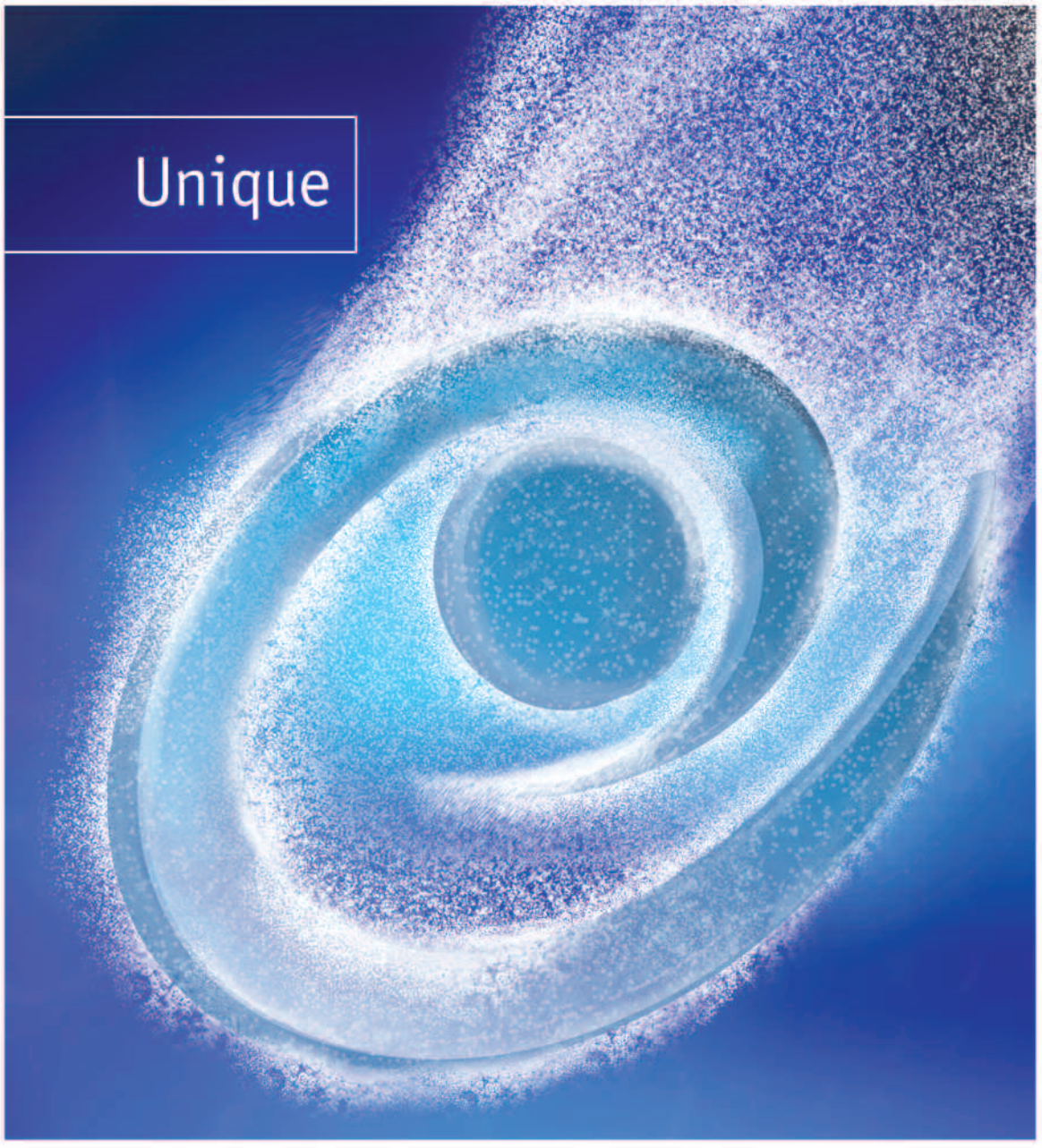
3M



"Depending on a final tally for the year, total investments in medical devices in 2007 may have reached $3.75 billion, a more than 40% increase from 2006. Combination products, which integrate a drug, a biologic, and/or a medical device into a single product, have emerged as an important segment of the well-funded medical device market."

p.36

Table Of Contents



Unparalleled taste Flexible dose Versatile release Robust tablet

AdvaTab® The next generation ODT

Eurand's AdvaTab is an orally disintegrating tablet (ODT) technology that combines superior taste and mouth feel properties in a robust tablet. AdvaTab is unique, offering both high dose capacity and modified drug release making it the most broadly applicable ODT available. Utilization of standard tabletting processes allows for cost-efficient manufacturing and conventional packaging. The next generation ODT is here!

EURAND

www.eurand.com

USA +01-937-898-9669
EU +39-02-95428-309

ODT CUSTOMIZED RELEASE TASTE MASKING ENHANCED BIOAVAILABILITY

CRO Strategies

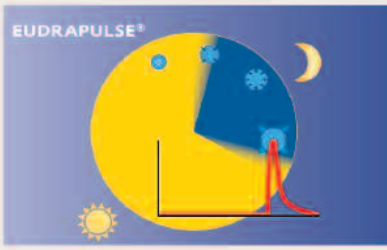
"Gone are the days of slow and expensive drug development cycles and large pharma's deep pockets for drug development. For many Specialty Pharma companies, success may hinge on a single compound and all of the company's resources are focused on pushing that compound through the development process as efficiently as possible."

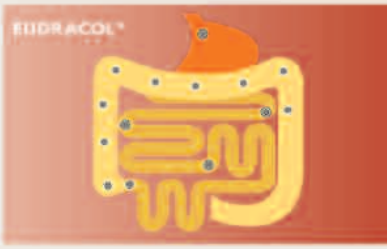
Table Of Contents

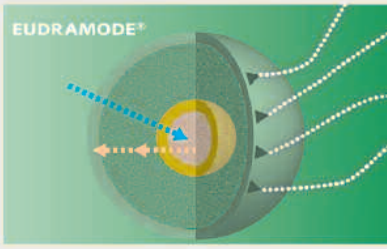
Don't miss your target! We offer tailor-made solutions for targeted release.

www.eudragit.com/drugdelivery

With EUDRAPULSE®, EUDRACOL® and EUDRAMODE®, Pharma Polymers has set new standards in advanced, proprietary oral drug delivery technologies. Our innovative solutions range from in-vivo proof of concept to customized product development. Combining our expertise with your business needs will give you a competitive edge to meet your targets.







For innovative product opportunities, contact us at:
Phone USA +1 732 981-5383
Phone Europe +49 6151 18-4019
www.eudragit.com/drugdelivery
www.evonik.com

Evonik. Power to create.

EVONIK INDUSTRIES

The EDITORIAL Advisory Board

Dan Marino, MSc
Executive Editorial Director
Drug Delivery Technology

WE DON'T JUST PROVIDE SOLUTIONS, WE CREATE SUCCESSFUL PARTNERSHIPS.

PharmaForm has an international reputation for developing novel solutions to challenging problems in pharmaceutical product development, manufacturing, and analytical testing. We specialize in working side-by-side with our clients, to deliver customized solutions to product development challenges. **Our Expertise. Your Advantage.**

Our Services:

- Formulation and Product Development
- Analytical Services
- GMP/GLP Manufacturing
- Method Development
- Validation Services
- Quality Control Testing and Stability Storage
- Reverse Engineering
- Patent Litigation Support
- Product and Platform Licensing Opportunities

GMP/GLP Compliant
FDA Registered/Inspected
DEA Licensed/Inspected

PharmaForm® L.L.C.
Excellence & Innovation in the Pharmaceutical Sciences

North America:
Michael M. Crowley, Ph.D., (512) 834-0449 ext. 202

International:
Josef Bossart, Ph.D., (512) 834-0449 ext. 278

Market News and Trends

Silence Therapeutics & AstraZeneca Announce Collaboration to Develop Novel Approaches for siRNA Drug Delivery

Silence Therapeutics plc recently announced a collaboration with AstraZeneca focused on the development of a range of novel approaches for the delivery of siRNA molecules. The deal builds on Silence Therapeutics' leading expertise in the delivery of siRNA molecules, in particular its success with the functional systemic delivery of siRNA in vivo using its proprietary AtuPLEX technology. The financial details of this collaboration, in which both parties will contribute expertise and know-how, have not been disclosed.

This new deal is independent of the parties' 3-year collaboration signed in July 2007, whose aim is to develop novel siRNA therapeutics against specific targets exclusive to AstraZeneca. As a result of the current agreement, Silence Therapeutics and AstraZeneca will work together to develop new and improved approaches for the delivery of siRNA molecules. The successful delivery of siRNA molecules to different tissue sites is critical to realize the exciting potential of siRNA to treat a broad range of diseases. Under the terms of the agreement, both Silence Therapeutics and AstraZeneca will be allowed to commercialize the truly novel delivery systems that they develop together.

"We are delighted to enter this new collaboration with AstraZeneca for the development of novel approaches for the delivery of siRNA molecules," said Jeff Vick, CEO of Silence Therapeutics. "This agreement highlights the significant progress we have made with our AtuPLEX platform, following our early realization of the importance of delivery to the development of successful RNAi therapeutics. This deal also reflects the strong working relationship we have developed with AstraZeneca and the progress of our ongoing collaboration in the development of AtuRNAi molecules against a number of their targets."

Mr. Vick continued, "We look forward to continuing our work with AstraZeneca in this important therapeutic area, and are extremely excited about the potential of our AtuPLEX delivery technology today and its ability to be developed further so that it can become an even more significant value driver for Silence Therapeutics."

Silence Therapeutics will retain the right to sign further delivery deals to capture value from its current AtuPLEX delivery technology as well as any improvements to this technology that it generates either independently or as part of this collaboration.

"We are very happy with the working relationship we have developed with the team at Silence Therapeutics and the progress made over the past 6 months via our agreement to develop siRNA therapeutics against a number of our targets," said Claude Bertrand, Global VP, Discovery Respiratory & Inflammation at AstraZeneca. "This announcement is designed to generate the novel delivery approaches that are needed if this exciting class of novel drugs is to realize fully its potential. Based on Silence Therapeutics' significant current expertise in siRNA delivery, we are confident that we have found a strong partner to achieve our ambitions in this area."

Silence Therapeutics plc is a leading RNAi company. RNA interference (RNAi) can selectively "silence" genes linked to the onset of disease. Silence Therapeutics has developed novel, proprietary short interfering RNA (siRNA) molecules, AtuRNAi, which provide a number of advantages over conventional siRNA molecules as they show increased stability against nuclease degradation. In addition, the company has developed a proprietary systemic delivery system, AtuPLEX. This enables the delivery of siRNA molecules to targeted diseased tissues and cells, whilst increasing their bioavailability and intracellular uptake.

In July 2007, Silence Therapeutics formed a research and development collaboration with AstraZeneca to develop AtuRNAi against five specific targets, including those in respiratory indications. The company's AtuRNAi technology also has been sublicensed to Pfizer through Quark's license to Pfizer of the compound RTP-801i-14 for the treatment of Age-Related Macular Degeneration (AMD) and a number of other indications. This compound entered the clinic in early 2007. Silence Therapeutics also has licensed to Quark rights to the AtuRNAi structure for its proprietary compound AKIi-5. This compound is in a Phase I human clinical study for treatment of acute kidney injury. In addition, Silence Therapeutics expects to begin the clinical development of its own proprietary AtuRNAi therapeutic molecules for systemic cancer indications in 2008. Silence Therapeutics is based in London and Berlin, and is listed on AIM.

We answered the cry.

Hydrophobic or hydrophilic.

Better ways to take your medicine.

NuSil Technology.

New drug delivery materials. They're making life-saving medicines easier to take. And that's helping save patients' lives, while improving their quality of life.

NuSil is proud to be part of it. As a leading provider of custom silicone solutions, our scientists are dedicated to helping innovators innovate.

From ingestible Simethicone to transdermal delivery materials, large batches or small, you can count on NuSil for precise, custom formulations, backed by nearly 30 years of healthcare expertise and extensive regulatory knowledge.

What? When? Where? If it's NuSil, it's no problem.

NuSil SILICONE TECHNOLOGY

What's your challenge?
www.nusil.com
USA 805-684-8780
Europe +33 (0) 4 92 96 93 31

EKR Therapeutics Raises Over $145 Million; Sees Recent Product Acquisitions Bolstering its 2008 Revenue Base

EKR Therapeutics, Inc., a specialty pharmaceutical company focused on acquiring, commercializing, and maximizing the potential of proprietary acute-care products, recently announced it has successfully completed the private placement of $50 million in Series D equity while also securing $95 million in senior debt.

The equity funding round was led by new investors MPM Capital and LLR Partners. Also participating were prior investors Quaker BioVentures and the Garden State Life Sciences Venture Fund managed by Quaker, as well as original institutional investors NewSpring Capital and ESP Equity Partners. The debt financing is being provided by GE Healthcare Financial Services.

As part of the equity financing, Steven St. Peter, MD, General Partner at MPM Capital, and Scott A. Perricelli, Partner at LLR Partners, have joined the EKR board of directors. In turn, the board has expanded to seven members, including five non-executive and two executive directors.

"The support of such a premier group of investors and lenders reflects a vote of confidence in EKR's business plan and is a testimony to the company's past successes and future prospects," said Howard Weisman, EKR's Chairman and CEO. "Since initiating operations less than 2 years ago, we have built a solid commercial organization with several on-the-market products and our own sales force. We are well positioned to enter the next stage of growth and to realize our goal of becoming the pre-eminent provider of specialty acute-care products."

Richard DeSimone, EKR Director and CFO, noted, "Our ability to access new, quality sources of capital and garner additional support from existing, leading healthcare investors is highly gratifying. Additionally, with these announced financing transactions, plus cash on hand, we have significantly enhanced EKR's flexibility to fuel the growth of our ongoing operations while pursuing strategic initiatives to bolster that growth."

A portion of the financing proceeds will be utilized to pursue acquisition candidates for EKR's portfolio of specialty acute-care products. That portfolio was recently enlarged by the first-quarter 2008 acquisitions of the Cardene franchise, including intravenous and oral formulations of this antihypertensive product, and Retavase, a drug for the management of acute myocardial infarction. Other product offerings from EKR include DepoDur, an injectable morphine acquired in August 2007 for the management of post-operative pain, and Gelclair, a bioadherent oral gel acquired in June 2006 for the treatment of oral mucositis.

"Through the application of our acquisition strategy, we have greatly enriched our product mix in the past few months and, correspondingly, our 2008 revenue base has been expanded by a factor of about 10," said Mr. Weisman. "Moreover, even if we exclude the potential for other product acquisitions in 2008, we foresee significant opportunities for organic growth off of this larger base. To this end, we plan to build upon and leverage the strengths of our field force to drive overall sales and maximize the synergies expected for our enlarged product portfolio."

EKR Therapeutics is a privately held specialty pharmaceutical company that has brought together a highly seasoned team of industry professionals. The company focuses on the acquisition, development, and commercialization of proprietary products to enhance patient quality-of-life in the acute setting, including cardiovascular, pain management, and oncology supportive care medications. From its inception in late 2005, EKR has been organized to be a class leader in commercializing products to address unmet and under-satisfied medical needs or to otherwise enhance the therapeutic value of acute-care prescription products. EKR's goal is to be the pre-eminent provider of specialty acute-care products, backed by a commitment to excellence in customer service and medical education programs.

Market News and Trends

Ceragenix to License CSA-54 and Other Ceragenin Compounds for HIV and STD Applications

Ceragenix Pharmaceuticals, Inc., a biopharmaceutical and medical device company focused on infectious disease and dermatology, recently announced it has entered into a license agreement with FirstPoint Biotech, Inc., a privately held biopharmaceutical company, for the development of CSA-54 and other members of the Ceragenin family of preclinical compounds for use as potential systemic and topical therapies in the treatment and prevention of HIV and sexually transmitted diseases. The agreement covers the potential use of these compounds as both drugs and incorporation into medical devices, such as condoms, sprays, or gels.

Pursuant to the terms of the agreement, FPBT will have the responsibility to undertake the clinical development and commercialization of these compounds within these fields of use, and Ceragenix will provide ongoing consultation. The agreement provides for payment of milestone payments and royalties. Additional financial terms were not disclosed.

As previously reported by the company, researchers from Vanderbilt University have found that CSA-54 potently inhibits HIV infection of primary human CD4+ T cells, the virus' in vivo targets, and was not toxic to epithelial cells at concentrations significantly higher than those required to kill the virus. In addition, CSA-54 killed a wide range of HIV isolates and completely blocked genetically engineered HIV that enters the cells independent of the cell surface receptor the virus normally uses.

"We are very pleased that development of CSA-54 as a potential therapy for the treatment and/or prevention of HIV will be continued," said Steven Porter, Chairman and Chief Executive Officer of the company. "Given our focus on antimicrobial coatings for medical devices, this was not an application that we could have pursued on our own."

Roslynne Flacks, Executive Chairman of FPBT, added, "Human immunodeficiency virus (HIV) infection in humans is now pandemic. According to current estimates, HIV is set to infect 90 million people in Africa alone, resulting in a minimum estimate of 18 million orphans. In the face of such a virulent enemy and the recent failure of vaccine trials, it is imperative that new approaches for preventing and treating this horrific disease be actively pursued. We believe that CSA-54 and other Ceragenin compounds may play a vital role in this effort, and we plan to use the resources of a leading contract research organization with experience in HIV drug development to accelerate the development of these promising compounds."

Ceragenix Pharmaceuticals, Inc. is a biopharmaceutical and medical device company focused on infectious disease and dermatology. The company has two base technology platforms: Ceragenins or (CSAs) for treatment of infectious disease and Barrier Repair for the treatment of dermatological disorders, including atopic dermatitis, neonatal skin disorders, and others. Ceragenin compounds are active against a broad range of gram positive and negative bacteria. The company has used its Ceragenin technology to formulate Cerashield antimicrobial coatings for medical devices. All Ceragenin and Cerashield products are currently in the developmental stage. Ceragenix's patented Barrier Repair technology, invented by Dr. Peter Elias, is the platform for the development of two prescription topical creams: EpiCeram and NeoCeram. EpiCeram has been cleared for marketing by the US FDA, and the company has entered into an exclusive supply and distribution agreement with Dr. Reddy's Laboratories for the marketing and sales of the product in the US. The company anticipates that DRL will launch EpiCeram during the second half of 2008.

FirstPoint BioTech Inc. specializes in innovation, research and development, and the deployment of proprietary breakthrough technology. FirstPoint is in the process of establishing a substantial intellectual property portfolio with international patents in a number of pharmabiotechnology areas.

Market News and Trends

Zogenix Seeks Investors for Needle-Free Injection Technology

Zogenix, a specialty pharmaceutical company, recently announced it has filed for an initial public stock offering. The California-based company, which is seeking to raise up to $86.5 million, is developing drugs for pain and central nervous system disorders.

Zogenix's lead drug to treat acute migraine is sumatriptan DosePro. The drug is delivered by its needle-free DosePro technology, which injects drugs under the skin with a pressurized dispenser. Patients can administer the drugs themselves with this technology. An application to sell the drug was accepted for consideration earlier this month by the US Food and Drug Administration.

Several companies have been developing needle-free drug delivery alternatives for medications, such as insulin. Because patients dislike needles, an effective and economical alternative is believed to have large market potential. But it's been difficult. Earlier this month, Eli Lilly & Co. dropped development of an inhaled form of insulin. Two other companies, Novo Nordisk and Pfizer, have dropped inhaled insulin products.

Zogenix is also testing a form of the drug hydrocodone for chronic pain that features time-controlled release and is taken orally. In its filing statement with the Securities and Exchange Commission, Zogenix indicated DosePro "has the potential to become a preferred delivery option for patients and physicians for many injected medicines beyond sumatriptan."

Drugs tested with DosePro include protein-based drugs, such as the anemia drug EPO; and monoclonal antibodies, several of which generate more than $1 billion a year in sales. Drugs for hepatitis, infertility, multiple sclerosis, and rheumatoid arthritis could possibly be delivered with DosePro, the filing statement indicated.

As of February 29, 2008, Zogenix reported having 27 full-time employees, divided between its Carmel Valley headquarters, which handles administration and marketing, and an office in Emeryville that performs drug development and manufacturing. Banc of America Securities LLC is managing the stock offering. Co-lead managers are Leerink Swann, Thomas Weisel Partners LLC, and Susquehanna Financial Group, LLLP. The registration statement is online at: http://tinyurl.com/28v2em.

Zogenix is a specialty pharmaceutical company whose goal is to uniquely enhance and differentiate medicines by incorporating innovative technologies in an effort to relieve suffering in people with CNS and pain disorders. Founded in 2006, the company currently has two proprietary product candidates in late-stage development. Its lead product candidate, sumatriptan DosePro, is a drug-device combination that enables needle-free delivery of subcutaneous sumatriptan, the fastest acting migraine medicine, for the treatment of migraine and cluster headache. Its second product candidate, ZX002, is a novel, oral controlled-release formulation of hydrocodone for the treatment of chronic pain.

Lilly Announces Termination of AIR Insulin Program

Eli Lilly and Company recently announced the termination of development of its AIR Insulin program, which was being conducted in partnership with Alkermes, Inc. The program has been in Phase III clinical development as a potential treatment for type 1 and type 2 diabetes. The company noted that this decision is not a result of any observations during AIR Insulin trials relating to the safety of the product, but rather was a result of increasing uncertainties in the regulatory environment, and a thorough evaluation of the evolving commercial and clinical potential of the product compared to existing medical therapies.

"This decision, though difficult, is the right one to make at this time," commented John Lechleiter, PhD, Lilly President and Chief Operating Officer. "Throughout the past several months, we have conducted a thorough review of all aspects of our efforts to develop our AIR Insulin product and have now made the decision that it would be inappropriate for the company to continue development activities in connection with this project. Without the prospect of a new drug application, keeping the patient foremost in mind, it would not be consistent with our medical principles to continue the clinical trials. As a result, we are now beginning the process of halting our ongoing clinical studies and transitioning the AIR Insulin patients in these studies to other appropriate therapies. We wish to reassure patients currently receiving AIR Insulin in our ongoing clinical trials that they should have no health or safety concerns about continuing to use AIR Insulin during their transition to other well-established diabetes therapies."

Steven M. Paul, MD, Executive Vice President, Science and Technology, for Lilly, added, "While we are confident in our decision, we also recognize the disappointment of those patients who saw the potential benefit of AIR Insulin." "As a leader in diabetes care, we remain committed to our mission to develop innovative, beneficial and cost-effective treatments for diabetic patients. It is also important to emphasize that our decision is not due to any safety concerns observed by Lilly or raised by the independent data safety monitoring board during our development of AIR Insulin."

Lilly is in the process of contacting the clinical investigators conducting the current AIR Insulin clinical trials. Subject to protocols, the trials will be halted, and the patients currently enrolled will be moved to other insulin therapy under the supervision of their physicians. In the US, Lilly will implement a patient assistance program to provide current clinical trial patients with appropriate financial support to fund their medications and diagnostic supplies through the end of 2008. Based upon further analysis, the company may also pursue a similar program in other regions.

As a result of the decision to terminate the development of AIR Insulin, Lilly will recognize a first-quarter 2008 charge to earnings related to the impairment of Lilly assets, as well as wind-down costs associated with the termination of clinical trials and certain development activities, and costs associated with the patient assistance program. The exact amount of the charge has not yet been determined, but is estimated to be in the range of $90 million to $120 million, or $0.05 to $0.07 per share. Lilly's pro forma adjusted earnings per share guidance remains unchanged at $3.85 to $4.00. On a reported basis, including the charge related to the termination of the AIR Insulin program, as well as the previously announced charge related to the BioMS in-licensing, Lilly now expects 2008 earnings per share to be in the range of $3.73 to $3.90.

Bilcare Global Clinical Supplies Appoints Vito Mangiardi as New CEO

Bilcare Global Clinical Supplies, the single source provider of quality clinical trial materials from formulation and analytical services to IVRS and global distribution spread across the Americas, Europe, and Asia, has appointed Vito Mangiardi, a 30-year industry veteran as the new CEO to lead the firm.

Speaking on this momentous occasion, Mr. Mohan Bhandari, Chairman & Managing Director, Bilcare Ltd., said, "Mr. Mangiardi is an exceptional leader and strategist. He has vast experience in global business management, pharmaceutical and biotech contract research and development services, and extensive expertise in clinical supplies. His breadth and depth of experience is unsurpassed in the industry, and he is a perfect fit for Bilcare GCS as we continue to experience steady growth."

According to Mr. Mangiardi, "This is an honor and tremendous opportunity for me to add value to this booming enterprise."

Mr. Mangiardi has gained a wealth of experience in virtually all aspects of the clinical supplies, pharmaceutical, and biotech industries. He has held key leadership positions throughout his career, most recently serving as President of North American Operations for AAI Pharma, where he was responsible for Phase I, formulation development, analytical development, bioanalytical, manufacturing and stability testing, as well as Phase II-IV clinical trials. At AAI, Mr. Mangiardi grew the revenue line significantly and turned the company results from a loss to a profit within 2 years.

Prior to his joining AAI Pharma, Mr. Mangiardi had a very successful career at Quintiles Transnational as a Senior Vice President and Chief Operating Officer of Global Phase IV Services. He also held other executive level positions at Quintiles, including head of the International Clinical Development Services group in Japan, head of the Asia Pacific Business and Executive Vice President of Operational Services of Quintiles Americas. Mr. Mangiardi has also served as President and CEO of Clingenix, Inc., an early stage pharmacogenomics company, and as President and CEO of Diagnostic Laboratories.

The addition of Mr. Mangiardi's expertise in pharmaceutical, biotech, and clinical supplies and services is another key element of a major global initiative that Bilcare GCS started in 2007. The initiative was undertaken to allow the company to provide a higher level of quality and service to its customers. During the past several months, the company has made substantial improvements globally, including upgrading equipment, increasing the number of its state-of-the-art packaging rooms, expanding its storage and distribution facilities, enhancing its formulation and analytical development services and technical capabilities, and integrating global operations.

Other key milestones in the global initiative were Bilcare's recent announcement of its commitment to invest in a state-of-the art clinical supplies facility in South Wales and the inauguration of the Bilcare Centre of Excellence in Pune, India. Wales is an ideal location for Bilcare GCS to service the European market at a competitive cost. It will strengthen what is already a key location geographically and strategically for Bilcare GCS. The Centre of Excellence in India will have dedicated R&D sections for Packaging Research, Material Research, Analytical Research, Drug Sensitivity Studies, and Package Design.

Glide Pharma Signs Biologicals Deal With Major Pharma Company for Solid Dose Injector

Glide Pharma, a specialty pharma company, has signed an agreement with a leading pharmaceutical company to evaluate its proprietary Glide SDI (Solid Dose Injector) technology for the delivery of a branded peptide product. This is Glide Pharma's third deal involving a biological product, with further agreements close to fruition.

The deal is described as a future-directed relationship, focusing initially on one of the pharma company's branded biologicals; the new partner has also taken an option to enter into a full development program. Under the terms of the deal, Glide Pharma will develop and test a range of solid dosage formulations of the branded peptide in the unique Glide SDI. These formulations will then be supplied to the partner company for further evaluation.

"With two existing agreements and a number in the pipeline, this latest deal with a major pharmaceutical company involving a branded biological is a significant step for us," said Glide Pharma's CEO, Dr. Charles Potter. "It also comes on the back of some very promising data on the administration of vaccines using the Glide SDI. This, together with our own drug development program, is beginning to build up a promising picture of the potential of the Glide SDI system as a commercially viable solution for administering both small molecules and biologicals, including vaccines."

By formulating the therapeutic or vaccine into a solid dose in the form of a tiny pointed rod that is "pushed" through the skin, the Glide SDI system does not require needles, so needle-stick injuries and needle-phobias are avoided. The solid dose is especially suitable for biological applications because storage in this form may avoid the need for refrigeration, and there are no reconstitution steps, making administration much easier for patients, caregivers, and healthcare professionals. Importantly the pen-sized, spring-powered actuator is small, lightweight, and easy to use, as well as being economical to manufacture.

Glide Pharma is a specialty pharma company focused on easy, safe, and convenient solid dose injection of therapeutics and vaccines. Using its proprietary Glide SDI system, Glide Pharma is building a pipeline of in-house and partnered products covering small molecules, biologicals, and vaccines. In 2007, Glide Pharma was the overall winner of the prestigious Medical Futures Innovation Awards for its Glide SDI - Solid Dose Injector.

Hovione Acquires Drug Manufacturing Facility in China

Hovione recently announced it has purchased 75% of Hisyn Pharmaceutical Co. Limited. The Zhejiang provincial authorities have already issued the necessary business license, and the joint venture (JV) is now operational.

The acquisition provides Hovione with significant additional drug substance manufacturing production capacity and strengthens its 20-year presence in China. It includes both development labs in Shanghai and an active pharmaceutical ingredient (API) plant occupying 22,000 square meters on a 22-acre plot employing 181 staff. Hovione's relationship with Hisyn started with the supply of intermediates, but this factory, which was commissioned in 2005 from a greenfield site, will now produce Hovione's two largest volume products.

"Hisyn represents an opportunity to both increase our manufacturing capacity and ensure a sustainable cost advantage," said Miguel Calado, CFO. "We find it important to provide our current customers with an assurance of competitive supply over the long run; and in addition, we want to have a strong presence in new markets, such as Brazil, India, and China, where price is decisive."

The negotiation and the acquisition processes moved smoothly in part due to the experience Hovione has built in China throughout the past 3 decades. The Macau plant, with 5 previous FDA inspections and more than 10 years of contract manufacturing relationships in China, has enabled Hovione to effectively bridge cultures with China in every dimension: language, GMP, culture, and business practices.

Luis Gomes, Vice President of Generics, and responsible for the investment and integration process, added, "When we first came to the Canton fair in 1979, we were buying raw materials that would be processed in Macau or in Portugal. For many years, we believed we'd be better off being an important client of Chinese plants through contract manufacturing deals because at that time there, many JVs were going very wrong. Now is the right time for Hovione to acquire infrastructure in China and tap into a growing market and leverage China's manufacturing abilities. We are planning to invest further monies in 2008 to effectively double Hisyn's manufacturing capacity."

Hovione is an international group specializing in the development and compliant production of active pharmaceutical ingredients, serving exclusively the pharmaceutical industry. In 2006, it had sales of $94 million. With almost 50 years in process development, quality standards, and advanced particle design technologies, Hovione offers APIs for all drug delivery systems, from oral to injectable and from inhalation to topical applications. With FDA inspected plants in Europe, the Far East, and New Jersey,

Hovione is committed to the highest levels of service and quality. Specializing in complex chemistry, Hovione offers services related to the development and manufacture of either a new chemical entity (NCE) for an exclusive contract manufacturing partner or an existing API for an off-patent product.

Flamel Suffers Greater Losses in 2007, Outlook Remains Optimistic

Flamel Technologies recently reported it has yet again experienced a net loss of $37.2 million for 2007, following a string of bad fortune in 2005 and 2006, but believes it may be about to turn the corner. The company remains optimistic that the success of GlaxoSmithKline's Coreg CR (carvedilol) heart medication, which makes use of Flamel's Micropump drug delivery technology, and a series of 10 new partnerships for its Medusa drug delivery platform, will turnaround its fortunes in 2008.

"We are satisfied with the results for 2007, and believe it puts us in a strong position for 2008," said Sian Crouzet, Flamel's Principle Financial Officer. "We have demonstrated our ability to adapt to the changing landscape."

During 2005 and 2006, Flamel experienced a series of misfortunes for its two drug delivery systems, including failed attempts by various pharmaceutical companies to use the systems for insulin and lansoprazole administration. These ultimately led to pre-tax losses of $9.6 million in the first quarter of 2006.

The fourth quarter revenue for 2007 included $2 million in milestone payments from GlaxoSmithKline, and $4.7 million from product sales and services compared to $2.1 million a year ago. Other revenue consisted of $2.4 million in royalty income from GlaxoSmithKline's Coreg CR product compared to $0.1 million in 2006. In total, this amounted to a revenue of $10.6 million compared to a revenue of $7.8 million a year ago.

Despite a string of cuts to its costs, this increased revenue still equates to a net loss of $5.4 million compared to $5.9 million a year ago for this quarter, and the net losses for 2007 are actually greater than 2006 ($37.2 million) compared to $35.2 million. It is thought that the company may have suffered from the poor exchange rate between the euro and the dollar.

However, it is hoped that the company's fortunes may be on the point of turning, with the success of the Micropump system for the Coreg CR drug demonstrating that the company's techniques are still viable methods of drug delivery, and the 10 new agreements with the Medusa platform demonstrating increased interest from the pharmaceutical industry.

"During 2007, a major focus of our company was to establish new relationships with interested partners and to develop our internal projects and technology platforms," said Stephen Willard, Flamel's CEO. "We succeeded in re-establishing and strengthening the Medusa platform by creating 10 new Medusa relationships, including those with Merck Serono and Wyeth. These relationships are a strong, well-diversified foundation for us to build the Medusa platform."

The fourth quarter also saw Flamel completing clinical trials for FT-105 basal insuling, and IFN-Alpha XL, the results of which are "compelling proof of concept for those two products," according to Mr. Willard. Flamel is now trying to license the products, which could eventually generate future revenue.

Morphotek Signs Exclusive Licensing Agreement for Anti-Cancer Antibody

Morphotek, Inc., a subsidiary of Eisai Co., Ltd, recently announced it has signed a licensing agreement with Human Monoclonals International, Inc. (HMI) for exclusive rights to a human monoclonal IgM antibody that is specific to a cancer cell surface antigen. Morphotek will apply its proprietary Morphodoma antibody technology and know-how with the goal of developing an optimized lead therapeutic monoclonal antibody and high-titer cell lines suitable for scalable manufacturing.

"This agreement provides yet another important addition to our therapeutic antibody portfolio," said Nicholas Nicolaides, PhD, President and Chief Executive Officer of Morphotek. "Safety data and positive clinical observations from an exploratory Phase I clinical trial in patients with metastatic melanoma have been reported. Our antibody optimization and development expertise will enable the further development of this promising antibody and clinical proof-of-concept studies in more types of cancer."

The in-licensed antibody was discovered through years of basic research focused on tumor cell biology and human cancer, in which researchers screened for naturally occurring antibodies made by the patient's immune system and discovered antibodies to several tumor-associated cell surface antigens. Antibodies discovered using this approach offer a means to isolate antibodies that recognize epitopes present on tumor antigens in their natural conformation. Epitopes are regions of an antigen that can elicit immune responses and can bind antibodies produced against the antigen. Morphotek will apply its antibody expertise to advance this optimized lead molecule into possible clinical trials in a variety of oncologic indications.

Morphotek, Inc. is a biopharmaceutical company specializing in the development of protein and antibody products through the use of a novel and proprietary gene evolution technology. The technology has been successfully applied to a broad variety of cell lines and organisms to yield genetically diverse offspring that are suitable for pharmaceutical product development in the areas of antibody therapeutics, protein therapeutics, product manufacturing, drug target discovery, and improved output traits for commercial applications. The company is currently focusing its platform on the development and manufacturing of therapeutic antibodies for the treatment of cancer, inflammation, and infectious disease.

MicroDose Technologies Grants Global License to Merck for Use of the MicroDose Inhaler

MicroDose Technologies Inc. recently announced it has entered into a global license agreement with Merck & Co., Inc., through an affiliate, for use of MicroDose's proprietary dry powder inhaler (DPI) with Merck compounds. This agreement follows the successful completion of an exploratory study evaluating the MicroDose DPI technology.

Under the terms of the agreement, Merck will fund development and commercialization of products that employ MicroDose's DPI technology for the administration of Merck compounds. MicroDose will receive an upfront payment and will be eligible for milestone payments totaling $32 million for successful development of the first product as well as royalties on product revenues. Additional products will also be eligible for milestones and royalties.

"We are delighted to expand our relationship with Merck, who have already proved to be very collaborative and decisive in their actions," commented Scott Fleming, Senior Vice President, Marketing of MicroDose. "This agreement to bring innovative inhalation products to market is a positive milestone in the continued growth of MicroDose and represents further validation of our DPI technology."

"Through this agreement, Merck has gained access to a novel delivery technology that has the potential to facilitate the administration of and ensure patient compliance with drug treatments targeting the lungs," said Soren Bo Christiansen, General Manager Bone, Respiratory, Immunology, and Endocrine Franchise, Merck & Co., Inc. "This approach is consistent with our leadership strategy of developing respiratory medicines that address unmet medical needs and deliver value to patients, physicians, and payers."

The MicroDose DPI is among a number of key proprietary drug delivery platforms developed by MicroDose. By employing piezoelectronics, the MicroDose DPI has the potential to deliver enhanced performance, versus other inhalers, for efficient and reproducible delivery independent of patient coordination, inhalation rate, and posture. MicroDose believes that the flexibility of the inhaler makes it a true platform technology, able to support a broad pipeline of products across the spectrum of patient populations and therapeutic categories.

MicroDose Technologies, Inc., based in Monmouth Junction, New Jersey, is a leading privately held drug delivery systems company, developing advanced pulmonary, fixed-dose-combination oral dosage, and other technologies for the pharmaceutical and biotechnology industries. MicroDose's partnered programs include a multi-product development and licensing agreement with Novartis, the development of an inhaled insulin product through MicroDose's QDose joint venture, and an inhaler for the systemic delivery of a nerve agent antidote for the US Department of Defense, in collaboration with the University of Pittsburgh. MicroDose is also conducting internal development programs for products employing its inhaler technology and for combination oral dosage products, employing its PolyCap technology, in the areas of diabetes, hypertension, and hyperlipidemia.

Azopharma Acquires Analytical Development Corporation; Announces Expansion of AvivoClin

Azopharma Product Development Group, Inc. recently announced the acquisition of Analytical Development Corporation (ADC), a bioanalytical laboratory located in Colorado Springs, CO, which will operate under the ADMEquant Bioanalytical Services name. ADC was founded in 1971 as a contract research organization providing quality bioanalytical services to the pharmaceutical and biotechnology industries.

The ADMEquant facility occupies 17,000 square feet of laboratory and office space, including 7,500 cubic feet of temperature-monitored freezer/refrigerator storage. The staff is composed of professionals averaging over 20 years of experience in analytical chemistry with expertise in ADME and metabolism studies.

According to Phil Meeks, Azopharma Chief Executive Officer, "The knowledge and experience at ADMEquant adds a lot to the Azopharma Product Development Group. Their experience supporting preclinical and clinical studies lifts the level of service and capabilities we can provide to our clients."

This latest acquisition enhances the extensive product development services from The Azopharma Product Development Group and provides a dedicated lab to support its preclinical and clinical projects.

Azopharma also announced the future expansion of its clinical pharmacology research facility, AvivoClin Clinical Services, located in Daytona Beach, FL. Azopharma introduced AvivoClin Clinical Services (formerly Coastal Medical Research) as a member of the Azopharma Product Development Group in January of this year. The expansion of the facility is scheduled for completion in late August 2008.

The expanded facility will include an additional 5,000 square feet, bringing the new facility to a total of 20,000 square feet. The patient bed capacity will also increase from 48 to 100 beds. According to Mr. Meeks, "The expansion of the AvivoClin facility allows us to grow our clinical services to better meet the growing needs of our clients. Through AvivoClin, Azopharma Product Development Group can support numerous clinical studies simultaneously resulting in a higher level of service to our clients."

The expansion of AvivoClin Clinical Services combined with Azopharma's latest acquisition of Analytical Development Corporation, now ADMEquant Bioanalytical Services, allows Azopharma Product Development Group to provide comprehensive clinical pharmacology services, which includes both clinical and analytical services. The expansion also further enhances Azopharma's ability to provide total product development services for pharmaceuticals and medical devices.

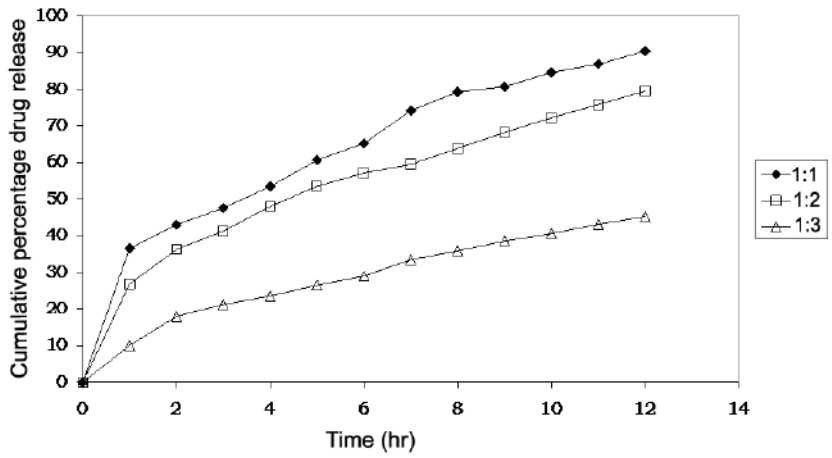
Mr. Meeks continues, "Azopharma Product Development Group is only one of a few organizations in the US that are capable of developing a full spectrum of dosage forms from discovery through commercialization. By bringing together the best scientists in the field, state-of-the-art facilities, and our focus on quality means that we can provide our partners a winning combination in total product development."

Influence of Drug-to-Lipid Ratio & Release Modifier on Dipyridamole Release From Floating Lipid Granules

By: V.F. Patel, PhD, MPharm, and N.M. Patel, PhD

This present investigation explores the application of Gelucire 43/01 for the design of multi-unit floating systems of a poorly water-soluble drug dipyridamole. Dipyridamole has higher absorption in a low-pH environment. Drug-Gelucire 43/01 granules were prepared by melt granulation with and without release modifiers. The granules were evaluated for in vitro floating ability and drug release. It was found that the granules had no floating lag time due to the extreme hydrophobicity of the lipids, irrespective of release modifier added. As the drug-to-lipid ratio increased, the release rate was decreased due to increasing thickness of covered layers of lipid on drug particles. The addition of release modifiers, sich as HPMC K4M, Ethyl cellulose (20 cps), PEG 4000, sodium chloride, sodium CMC, and Sterotex NF, in lipid matrices showed increase in drug release with an increased burst effect, except ethyl cellulose. Kinetics of drug release showed a release mechanism shift from case-I transport to anomalous release depending on drug-to-lipid ratio and release modifier added. In conclusion, hydrophobic lipid, Gelucire 43/01, can be considered an effective carrier for the design of a multi-unit floating drug delivery system, and release of drug can be modified by the addition of various release modifiers.

FIGURE 1



Influence of drug-to-Gelucire 43/01 ratio on drug release from floating granules.

INTRODUCTION

Rapid gastrointestinal (GI) transit could result in incomplete drug release from the device above the absorption zone, leading to diminished efficacy of the administered dose.[1] Therefore, different approaches have been proposed to retain the dosage form in the stomach. These include bioadhesive systems, swelling and expanding systems, and floating systems.[2] Large single-unit dosage forms undergo significant swelling after oral administration, and the swollen matrix inhibits gastric emptying even at an uncontractile state of the pyloric sphincter. Park and Park reported medicated polymeric sheets and swelling of balloon hydrogels.[3] However, the swelling and expanding systems may show hazard of permanent retention. Bioadhesive systems may cause problems, such as irritation of the mucous layer owing to high localized concentration of the drug.[4] Hydrodynamically balanced systems, designed using effervescent mixtures, have achieved commercial success but require a high drug:excipient ratio, have unpredictable bioavailability, and are unsuitable for drugs degrading in basic pH due to the alkaline microenvironment. Single-unit systems, such as tablets or capsules, may exhibit the all-or-none emptying phenomenon, which may be overcome by the design of multi-unit systems. Multi-unit dosage forms, such as pellets and granules, may be more suitable because they claim to reduce the intersubject variability in absorption and lower the probability of dose dumping.[5]

Gelucire is a family of vehicles derived from mixtures of mono-, di-, and triglycerides with polyethylene glycol esters of fatty acids. Lipids are considered an alternative to polymers in the design of sustained drug delivery systems due to their advantages, such as low-melt viscosity (thus avoiding the need of organic solvents for solubilization), absence of toxic impurities (such as residual monomer catalysts and initiators), potential biocompatibility, and biodegradability. Gelucires are available with a range of properties depending on their Hydrophilic Lipophilic Balance (HLB 1-18) and melting point (33°C to 65°C) range.[6] Gelucires containing only

Pharma Ingredients & Services

Custom Synthesis
Excipients
Active Ingredients

Dr. Anisul Quadir
an enabler in pharmaceutical development

Dr. Anisul Quadir is ready to face the toughest challenge. Yours.

As head of technical services in North America for BASF, Dr. Anisul Quadir and his team are committed to providing customer specific solutions to the toughest formulation and manufacturing challenges. With access to state of the art equipment and technical expertise, they enable cost-effective solutions that can take you from early-stage development and process improvement, right through to scale-up operation.

Simply contact us today, and let Dr. Anisul Quadir and his team enable a custom solution for you. Call technical services at 1-800-469-7541.

Contact us via e-mail at pharma-ingredients@basf.com
or visit www.pharma-ingredients.basf.com

BASF
The Chemical Company

Pharma Ingredients & Services.
Welcome to more opportunities.

PEG esters (Gelucire 55/18) are generally used in preparation of fast-release formulations, while Gelucires containing only glycerides or a mixture of glycerides and PEG esters (Gelucire 54/02, 50/13, 43/01) are used in preparation of sustained-release formulations.[7] Sutananta and co-workers reported sustained-release single unit matrices using Gelucire 43/01 in which only 1.7% theophylline was released over a period of 20 hours.[8] In vivo floating ability of low HLB Gelucire matrices were well established.[9,10]

Dipyridamole is a poorly soluble weak base with a reported pKa of 6.4, and was reported to be altered to a considerable extent by the pH of different digestive fluids, hence dipyridamole dissolves readily in the stomach but incompletely in intestine.[11] A study by Miyazaki and co-workers reported that the extent of absorption of dipyridamole is remarkably lower when gastric pH was continuously elevated to 6.0, whereas it was increased when gastric pH was temporarily decreased to 1.8, which might be due to the contribution of precipitation potential of drug when pH was changed from the acidic to neutral region.[12] Due to the aforementioned dipyridamole bioavailability, it would be beneficial to develop a floating drug delivery system that will prolong gastric residence time and release drug in the proximal GI tract in which absorption of dipyridamole is more confined.

MATERIALS

Dipyridamole was a generous gift from Sun Pharmaceutical Ltd. Gelucire 43/01, Gelucire 50/02, and Compritol ATO 888 were a generous gift from Gattefosse. HPMC K4M and Ethyl cellulose 20 FP were kindly supplied by Colorcon Asia Pvt Ltd. Sterotex NF was supplied by Abitec Corporation. Sodium CMC, PEG 4000, and sodium chloride was procured from Lesar Chemicals.

METHODS

Preparation of Floating Granules

Floating granules containing dipyridamole were prepared using the melt granulation technique. The drug: lipid (Gelucire 43/01) ratios used to prepare the different formulations were 1:1, 1:2, and 1:3. To study the effect of release modifiers, such as HPMC K4M (4000 cps), Ethylcellulose (EC, 20 cps), PEG 4000, Sodium CMC, sodium chloride, and Sterotex, NF (hydrogenated cotton seed oil, white solid powder, mp 61.4°C, HLB = 1.5) were added separately to the formulations. The proportion of additives was 0.5 parts for HPMC and EC, Sodium CMC, and sodium chloride, whereas it was 0.25 parts for PEG 4000 and Sterotex. Lipid was melted at 50°C, and the drug or drug and additives mixture was added, mixed well, and cooled to room temperature. PEG 4000 and Sterotex were melted previously before addition to the melted lipid. The mass was solidified and passed through a 510-micrometer sieve to obtain uniform-size granules.

TABLE 1

Drug-to-Gelucire Ratio	Release Modifier	Kinetic Parameters		
		n	k	R^2
1:1	-	0.394	0.333	0.986
1:2	-	0.433	0.264	0.998
1:3	-	0.574	0.109	0.995
1:2	HPMC K4M	0.408	0.298	0.994
1:2	Ethyl Cellulose	0.563	0.174	0.997

Regression output for dissolution profiles treated with Korsmeyer and Peppas equation.

In Vitro Evaluation of Floating Ability

Fifty-unit granules were placed in 900 mL of distilled water and 0.1 N HCl (pH 1.2) in a vessel maintained at 37°C ± 0.2°C and stirred at 50 and 100 rpm in a USP 24 type II dissolution test apparatus (Electrolab TDT-06P). The percentage of floating granules up to 8 hours was determined, and the floating times were measured by visual observation.[1]

In Vitro Drug Release Studies

The release of drug from the granules containing different drug-to-lipid ratios and formulations containing different release modifiers was investigated in triplicate. Studies were performed in a USP 24 type II dissolution test apparatus with an agitation speed of 100 rpm in 0.1 N HCl (pH 1.2) maintained at 37°C ± 0.2°C. At appropriate time intervals, samples were withdrawn and assayed spectrophotometrically at 283 nm with suitable dilutions (UV-2401, Simadzu Corporation). Standard deviation among the data was below 3%, therefore, only average value was considered.

RESULTS & DISCUSSION

The melt granulation technique was employed for preparation of dipyridamole floating granules using lipid matrices. For floating granules, Gelucire 43/01 (mp 43°C, HLB 01), Gelucire 50/02 (mp 50°C, HLB 02), and Compritol ATO 888 (mp 70°C, HLB 02) were tried. Among these lipids, Gelucire 43/01 has shown a desirable floating property with retardation of drug release, while the granules prepared using Gelucire 50/02 and Compritol ATO 888 sink inside the dissolution medium and release the drug within 1 hour. Gelucire 43/01 comprises a mixture of hemi-synthetic glycerides of different fatty acids. Extreme hydrophobicity of Gelucire 43/01 is attributed to the absence of PEG esters, which in turn provides release-retarding ability. The hydrophobic nature of the excipients is thus responsible for the floating behaviors, but all excipients with low HLB did not ensure the floating property as shown by Gelucire 50/02 and Compritol ATO 888, which indicates (apart from hydrophobicity), density also plays an important role in designing floating matrices using lipid excipients. Hence, the study was restricted to Gelucire 43/01.

No significant difference was observed in the floating ability of granules containing different proportions of Gelucire 43/01. All granules were floated for more than 8 hours. However, the drug release retarded significantly with an increase in the amount of Gelucire (Figure 1). The drug-release profile of drug-to-lipid ratio of 1:1 showed burst release in the initial period, but an

We know why it pays to be correctly formulated

At SOLIQS, we approach the pharmaceutical formulation challenge a little differently than others. We understand that as a formulator or manager responsible for drug development at your company, bioavailability may be a primary focus for your increasing number of poorly soluble candidates and compounds. But we also know that getting the right formulation early on can have a major impact on the development of a product and its future success. From optimizing release, to reducing PK variability, to increasing tolerability and minimizing side-effects, to improving stability and scalability, the right choices will help to safeguard your products against the challenges of the commercialization process.

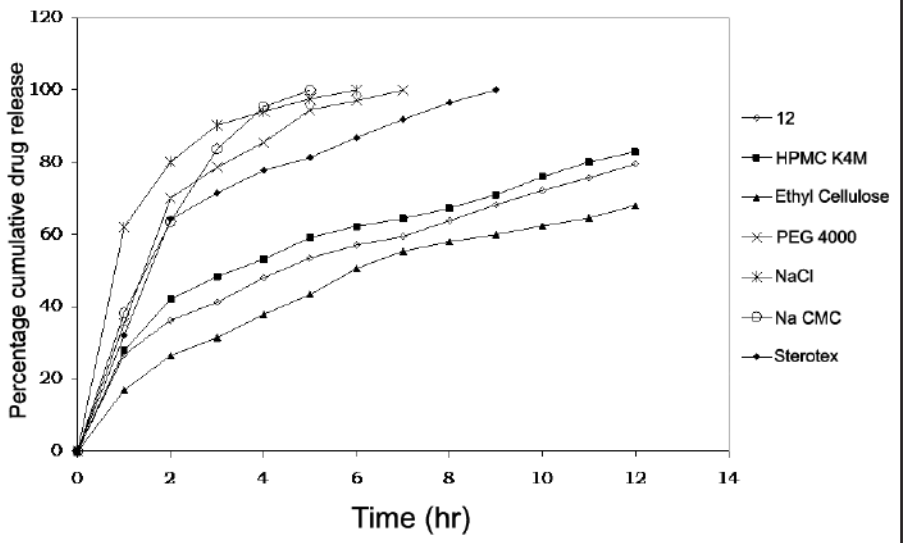
We have a broad and flexible portfolio of proven drug delivery solutions that can help you make these choices, including SOLIQS Meltrex®, our proven melt extrusion technology.

To find out more, visit www.soliqs.com or call us on +1 877 765 4771 (US) or +49 621 599 2554 (Worldwide).

Soliqs
SOLIQS

SOLIQS is the Global Drug Delivery Business of Abbott GmbH&Co.KG

FIGURE 2



Influence of release modifiers on drug release from floating granules prepared using drug-to-Gelucire 43/01 ratio of 1:2.

increase in lipid ratio above 1:2 caused significant retardation of drug release, making it unsuitable for gastroretentive drug delivery in which complete drug release was expected within 10 to 12 hours. The granules containing a drug-to-lipid ratio of 1:3 showed significant retardation with only 45.17% drug release in 12 hours. Hence, the higher level of lipid in the present study was restricted to 1:2. Granules prepared with a drug-to-lipid ratio of 1:2 were evaluated for further study. It was also observed that there was no effect of agitation speed on floating behaviors as the granules were floated without lag time for the entire study.

In an attempt to modify the drug-release kinetics, various release modifiers were tried, namely HPMC, EC, PEG 4000, sodium CMC, sodium chloride, and Sterotex, in granules containing a drug-to-lipid ratio of 1:2. The granules prepared with the addition of PEG 4000, sodium CMC, and NaCl did float on dissolution medium, but started to sink within 30 minutes. This might be due to the high density of additives used a well as rapid leaching of PEG 4000 and NaCl due to their higher solubility, making the lipid structure fill with water, sink, and completely release drug within 6 hours in the case of NaCl and 7 hours in the case of PEG 4000 with high initial drug release of 80.10 % and 70.10% within 2 hours, respectively (Figure 2). Similar observation was also reported by Paradkar and co-workers.[13] They reported that PEG 4000 leached rapidly from the single-unit matrices prepared using glyceryl monooleate to create pores and channels through which dissolution fluids enter, thus accounting for increased initial burst release and overall release rate. Granules containing sodium CMC also showed similar behavior, which might be due to the rapid swelling and high density of the polymers, leading to the opening of channels for drug to get dissolved and diffuse out from hydrophobic matrices. Complete drug release was occurred within 5 hours with rapid release of 63.3% in the first 2 hours.

The addition of HPMC, EC, and Sterotex did not alter the floating ability of lipid granules. Drug release was increased with the addition of HPMC with an initial increase in burst release compared to plain drug-lipid granules, but sustained the drug release for a period of more than 12 hours (Figure 2). Although HPMC K4M is often used as a controlled-release matrix carrier, its combination with Gelucire 43/01 did not display a combined effect. The immiscibility between the hydrophobic wax and the hydrophilic polymer may hamper the performance of each material to function as a release retardant. The continuity of the hydrophobic domain of wax was interrupted by the swelling of cellulose polymer, leading to faster drug release from granules than from the granules without HPMC K4M.[14] A low-density HPMC and high-strength gel formed upon contact with the dissolution fluid, and the granules were able to maintain their floating property while releasing drug for a longer period of time. This was not observed with sodium CMC, which might be due to the high-density weakened gel formation (by sodium CMC) resulting in the rapid erosion of matrices.

Granules containing ethyl cellulose showed retardation of drug release with a decreased initial burst without hampering floating ability (Figure 2). The surface hydrophobicity imparted to the drug particles by the polymer and lipid synergistically decreased the drug release.

The addition of Sterotex to granules showed rapid release of drug in the initial phase, with 64.2% drug released within 2 hours, and remaining drug was released for a total period of 9 hours. Although Sterotex is hydrophobic in nature having an HLB value of 1.5, the granules prepared upon its addition to lipid did not ensure uniform covering of the surface of drug particles by Gelucire 43/01 due to the difference in melting points of both substances, which leads to non-uniform distribution and weakening of the bonding of lipid particles and increased drug release.

The dissolution profiles were fitted to an equation offered by Korsmeyer and Peppas.[15] Kinetic treatment was only applied to formulations containing various lipid ratios and granules containing HPMC and EC, as the remaining batches gave more than 60% release within 2 hours. Kinetic treatment revealed that the mechanism of drug release was shifted from case-I transport to anomalous behavior as n values were seen in the range of 0.394 to 0.574, depending on the drug-to-lipid ratio and the release modifier added (Table 1). Granules with a drug-to-lipid ratio of 1:1 had an n value of 0.394, indicating case-I transport or fickian diffusion. As the drug-to-lipid ratio increased from 1:2 to 1:3, the diffusion exponent value was found to be 0.443 and 0.574, respectively, which indicates anomalous release. The observed effect might be due to more uniform covering of drug particles upon increasing lipid levels. The addition of

HPMC in granules exhibited an n value of 0.408, which indicates fickian diffusion with increased drug release due to the hydrophilic properties of release modifier with an increased release-rate constant. Granules containing EC showed an n value of 0.563, which indicates anomalous behaviors and explains the increased release restriction provided by the hydrophobic release modifier with decreased release-rate constant.

Overall, it was observed that as the drug-to-Gelucire 43/01 ratio increased, the release-rate constant decreased. Also, the addition of HPMC leads to increased release-rate constant, and EC showed decreased release rate of drug.

CONCLUSION

Owing to its extreme hydrophobicity and low density, Gelucire 43/01 may be considered an appropriate carrier when designing a floating drug delivery system of dipyridamole.

ACKNOWLEDGEMENT

The authors are thankful to Sun Pharmaceutical,Vadodara for providing gift samples of dipyridamole, Colorcon Asia Pvt. Ltd., Gattefosse, Cedex, and Abitec Corporation, for providing gift samples of excipients.

REFERENCES

1. Iannuccelli V, Coppi G, Bernabei MT, Cameroni R. Air compartment multiple-unit system for prolonged gastric residence. part I: formulation study. Int J Pharm. 1998; 174:47-54.
2. Yeole PG, Khan S, Patel VF. Floating drug delivery systems: need and development. Ind J Pharm Sci. 2005;67(3):265-272.
3. Park K, Park H. Enzyme digestible balloon hydrogel for long-term oral drug delivery: synthesis and characterization. Int Symp Rel BioactMater. 1987;14:41-42.
4. Ching HS, Park H, Kelly P, Robinson JR. Bioadhesive polymers as platform for oral controlled drug delivery. part II. synthesis and evaluation of some swelling water-insoluble bioadhesive polymers. J Pharm Sci. 1985;74:399-405.
5. Efentakis M, Koutlis A, Vlachou M. Development and evaluation of oral multiple-unit and single-unit hydrophilic controlled-release systems. AAPS PharmSciTech. 2000;1(4):E34.
6. Aïnaoui A, Vergnaud JM. Modelling the plasma drug level with oral controlled release forms with lipidic Gelucire. Int J Pharm. 1998;169:155-162.
7. Dennis AB, Farr SJ, Kellaway IW, Taylor G, Davidson R. In vivo evaluation of rapid release and sustained release Gelucire capsule formulations. Int J Pharm. 1990; 65:85-100.
8. Sutananta W, Craig DQM, Newton JM. An evaluation of the mechanisms of drug release from glycerides bases. J Pharm Pharmacol. 1995;47:182-187.
9. Chauhan B, Shimpi S, Mahadik KR, Paradkar A. Preparation and evaluation of floating risedronate sodium Gelucire 39/01 matrices. Acta Pharm. 2004;54:205-214.
10. Chauhan B, Shimpi S, Mahadik KR, Paradkar A. Preparation and evaluation of diltiazem hydrochloride-Gelucire 43/01 floating granules prepared by melt granulation. AAPS PharmSciTech. 2004;5(3):article43.
11. Kohri N, Miyata N, Takechi S, Nomura A. Evaluation of pH-independent sustained release granules of dipyridamole by using gastric acidity controlled rabbits and human subjects. Int J Pharm. 1992;81:49-58.
12. He X, Kadomura S, Takekuma Y, Sugawara M, Miyazaki K. A new system for the prediction of drug absorption using a pH controlled Caco-2 model: evaluation of pH-dependant soluble drug absorption and pH-related changes in absorption. J Pharm Sci. 2004;93:71-77.
13. Kirankumar M, Shah MH, Ketkar A, Mahadik KR, Paradkar A. Effect of drug solubility and different excipients on floating behaviour and release from glyceryl monooleate matrices. Int J Pharm. 2004;151:151-160.
14. Lin J, Zhang F, McGinity JW. Properties of lipophilic matrix tablets containing phenylpropanolamine hydrochloride prepared by hot-melt extrusion. Eur J Pharm Biopharm. 2001;52:181-190.
15. Peppas NA. Analysis of fickian and non-fickian drug release from polymers. Pharm Acta Helv. 1985;60:110-111.

BIOGRAPHIES

Dr. Viral F. Patel is a Research Associate in the Formulation Development Department at the Pharmaceutical Technology Centre, Cadila Healthcare Limited, Ahmedabad (India). He has 10 publications to his credit in various national and international journals. Dr. Patel has completed his PhD in Pharmaceutical Sciences at Hemchandracharya North Gujarat University, Patan (India).

Dr. N.M. Patel is currently Principal and Professor at Shri B.M. Shah College of Pharmaceutical Education and Research, Modasa (India). He is Dean of Faculty of Pharmaceutical Sciences and an approved PhD guide at Hemchandracharya North Gujarat University, Patan (India). He has 28 years of academic and research experience, published 15 research papers in national and international journals, and authored three books.

MBO Discussion Series

Financing the Purchase: Where Will it Come From?

Part III of The Born-Again Entrepreneur (February 2008)

By: Derek G. Hennecke, MBA

You want to buy the company. You have a fair idea of what it's worth, and it's a safe bet that your checkbook has probably never seen that many zeros. You're probably suffering from a major case of sticker shock. Here's where I help you figure out how to come up with the cash, right?

Well, not just yet. It appears there are just a few other add-ons you're going to have to consider before you start scrambling for change under the couch cushions.

When the seller agrees to sell to you, he's not going to give you anything but the basic operation. He's certainly not going to front you the money to pay the salaries that come due the next day, or the photocopy repair man, or the inventory delivery on the doorstep. Any additional working capital he has, any CDs he holds in reserve, he's going to take with him. So would you in his shoes, right? You're going to inherit the business stripped bare. What you'll need is working capital – money to run the business regardless of what and when sponsors pay you and preferably some reserves as well.

How much working capital will you need? The best way to get a feel for this is to go over the company's past year or two of cash flow and profit-and-loss reports. Fortunately, the pharmaceutical business isn't seasonal, so you don't have to cover the ups and downs. You should, however, look at how quickly sponsors pay their bills.

If your plan is to grow the business, you'll need to raise additional capital to invest in new lab equipment, qualify it, and get people trained before you can run it and get some return on that equipment. When I took over Xcelience, this was a huge priority for me – not just so I could sleep at night, but also to invest immediately and send a message to sponsors and employees that we were in business and the future was bright.

So start with the purchase price, add your working capital, investment capital, and a healthy reserve, and you

Penwest Oral Drug Delivery Technologies Now Available at Pii

TIMERx®
Controlled Release Delivery Systems

- Commercialized Technology
  - *Recently approved in a BID pain product in the U.S.*
  - *Previous approvals in cardiovascular and incontinence products in Europe and U.S.*
- Easy to scale-up and manufacture
- Precisely controls drug release
- Cost effective

Geminex®
Dual Drugs, Dual Releases

Dual-delivery system for the customized release of two drugs.

SyncroDose™

Releases drug at the desired site along the GI tract.

GastroDose™

Retains formulation in the stomach for absorption from the upper GI tract.

For more information on any of these technologies, please contact Penwest at:

Phone: 203-796-3700
Fax: 203-794-1393
Email:bizdev@penwest.com
www.penwest.com

Penwest

Pii

Penwest's collaboration with Pii includes formulation, scale-up and manufacturing utilizing Penwest's technologies for its clients.

have the round figure you need to raise. It is not unreasonable to consider the need to have reserves enough to cover a full 4 to 5 months of costs if you had to. Now if you can just manage to peel your fingernails off the ceiling, we'll talk about where those funds might come from.

First, assess what you can throw into the pot. No matter what any book has told you, you're going to have to put some of your own cash into the game. The banks and investors are going to want to see some real equity – meaning cash you own, not cash you've borrowed. They want you to have skin in the game. It's not that they actually *need* whatever small amount you're able to scrape together; they want to know that if things go bad, you'll stick with it to the bitter end.

Another place to look, believe it or not, is at the guy who's trying to sell to you.

In some cases, sellers may be willing to "carry back" part of the purchase price. This quite simply means that he might loan you some of the money you need to buy the company. This is great, when it works. Some sellers will carry back as much as 20% of the purchase price. It even gives you some leverage to recover funds if the seller fails to adequately live up to parts of your bargain.

However, there are two big drawbacks to this approach in your situation. First, if you have any competition to buy the business, throw this option out the window. Sellers will rarely consider carry backs if they have other options. Second, in an MBO, your leverage in recovering funds for indemnifications is pretty much nil anyway because you ran the place before buying it, so the seller is just going to point the finger at you.

Remember, the cardinal rule (no, not that Cardinal) is that an MBO has an advantage because it offers something to the seller that other buyers don't. One of the big benefits for a seller in selling to its managers is that it has little due diligence to do and few hassles going forward.

Our next source of funds is family and friends. I mention this with a hefty caveat – you need to take responsibility for the sophistication of your investors. Don't let Uncle Bill give you his entire retirement savings. You should also recognize that while the in-laws may pony up $10,000, they are likely to monopolize a lot more than their share of telling you what to do.

In the end, we didn't go to family. My wife was willing to risk losing everything *we* had, but she didn't want the embarrassment of having to call Uncle Bob if we got into trouble.

If you do go the family route, the money may be presented either as a gift or a loan. If it is a gift, the bank will probably require a letter from the giver stating that it in fact, is a gift. If it's a loan, know that the bank will almost certainly ask you to go back to the family and get them to sign documents subordinating family loans to theirs. That means that if the business tanks, the bank gets paid first.

Employees are a great source of equity. Again, they probably don't have a lot of cash, but anything they can put in contributes to their own sense of ownership and shows other potential investors the level of confidence you have from inside the company.

You will also need to start looking for other outside investors. Put the word out. Ask within the banking community, look to disheartened real estate investors, or just get in touch with people you know to be "connected" for leads. I belonged to a local entrepreneurial club called the Renaissance Forum, which gave me several contacts both for financing and general advice about the whole MBO.

For the rest, you borrow. I mention this last because the banks like to know about your other sources when you approach them, but in reality, you want as much debt as possible as long as you can support the interest payments in the worst times. Debt will always be cheaper, assuming you will earn a higher rate of interest than you

would pay in interest. And if you won't be earning more than you'd pay in interest, you shouldn't be considering an MBO. Your money is better off in the bank.

So on to the bank. The first thing you're going to need if you're even going to open a conversation with these guys is collateral. Very rarely will banks lend without collateral *if* the loan is guaranteed by the Small Business Administration (SBA). I'm told the SBA goes through cycles of being open to lending, and being very tight. If you want to try this route, be aware that the SBA is not going to back a loan in which the buyer has no industry experience or no skin in the game. In the vast majority of cases though, collateral is your starting point.

An obvious source of collateral is your home equity. Better still are the assets of the company you're about to purchase. This is how I raised most of the capital I needed. If your company owns a lot of hard assets like equipment, particularly a few large expensive pieces, the bank may be willing to loan against these. If these assets already have loans against them, you may be able to assume the loans. Remember though that assuming a loan is the same as paying the seller that amount of money.

Shop around. You'd be amazed at the differences between what several banks will offer you. Like everything else in life, the lowest cost is not always the best deal. Try your best to find a bank with the right chemistry.

Here's one more crazy idea for financing that may just not be so crazy if the amount of cash you need isn't too high. Over the last 2 years I've been shocked by the number of entrepreneurs I know who have actually started their companies with credit cards. Think about it for a minute. How many credit card offers do you get every week? What if you applied to five of them and took cash advances? There you go, a usury loan at 22% no less but still cheaper than private equity. I have one friend who got $100,000 for an MBO this way.

Still another source is private equity financing. I won't delve into this topic, partly because there is so much to cover, but also because we didn't go down this route.

Once you have the financing package, take it for a test drive. Put together a monthly spreadsheet for at least 3 years looking at the P&L and cash flow and making sure you will be able to keep up your payments. Then throw in some bends – what if sales drop by 30%?

Finally, try to create some wiggle room for yourself above and beyond the finance package. Ideally, get the banks to okay a nice roomy line of credit. I must've interviewed a dozen banks before I found one that was willing to give me a line of credit, I then camped out on their doorstep in the days before the deal went through to make sure it all went through in time, but that line of credit has been a great stress valve. It also gave me some competitive agility in those early days. If I saw an opportunity, I knew I could pounce on it before the competition because I had the funds already available. It's this kind of flexibility that makes the whole takeover fun and not a shortcut to an early heart attack. ◆

BIOGRAPHY

Derek G. Hennecke, MBA
President & CEO
Xcelience

Mr. Derek G. Hennecke is a founding member of Xcelience. From 2004 to 2006, he served as Vice President and General Manager, Pharmaceutics and Biopharmaceuticals of MDS Pharma Sciences, Inc. In this capacity, he was responsible for the business and operations of MDS' CRO formulation development, including capsule development, tablet formulation, modified-release tablets, suspensions, solutions, suppositories, creams, ointments, and gels. Prior to joining MDS, Mr. Hennecke held various drug development management positions for DSM in Canada, Egypt, The Netherlands, and Mexico. In these roles, he built the operations or businesses to introduce various drug products for Europe and the US. Mr. Hennecke has also worked for Roche's research activities in Germany and Canada. He earned his BSc from the University of Alberta (Canada) and his MBA at the Erasmus University in Rotterdam, (The Netherlands).

Obviousness - The Subject That Just Won't Go Away

By: Clifford M. Davidson, Esq.

My previous two discussions concerned the Supreme Court's holding in *KSR International v. Teleflex Inc.*, 127 S. Ct. 1727 (April 30, 2007), which will be referred to as the KSR decision. This subject continues to dominate the world of intellectual property. This is a reflection of the importance of the determination of whether an invention is obvious. Patent attorneys do not argue black and white. Black and white arguments center around the novelty of an invention, with the question to be answered being "is there any one piece of prior art that describes the elements in the claim completely?" Patentability is typically a shade of gray. In the gray area, we consider whether the combination of multiple references (ie, multiple pieces of prior art) fairly teach or suggest all of the elements in the patent claim being considered. The standard for making the obviousness/non-obviousness determination determines the patentability of most inventions. When there is a shift in how this determination is made, the predictability of patentability of inventions changes. The following discussion seeks to further explore the determination of obviousness in a post-KSR world.

First, a few statistics. Since the KSR decision was published on April 30, 2007, there have been 19 decisions concerning obviousness by the Court of Appeals for the Federal Circuit, which hears all patent appeals from the US District Courts. Of the 19 decisions, 13 reached a decision on obviousness (5 cases were remanded to the District Court for further evidence concerning the issue of obviousness, etc). Nine of the 13 decisions held that the patent claims were valid and not obvious. Three of the 9 decisions reversed a determination by the District Court to arrive at the decision of non-obviousness. Ten of the 13 Federal Circuit decisions that reached the determination of obviousness upheld the District Court's determination. These numbers suggest that the Federal Circuit is upholding determinations of the District Courts at a greater percentage than previously.

Of the 13 decisions by the Federal Circuit on Pharma cases, 10 concerned Pharma inventions. Interestingly, 9 of these 10 decisions upheld the patent (the claims were deemed not obvious). It is too early to tell if this is a trend or merely an aberration of an overall trend.

A clear trend is emerging from the USPTO Board of Patent Appeals and Interferences, which hears appeals of final rejections made by the USPTO Examiners. Since the KSR decision, 101 cases have been heard by the Board of Appeals. In 74 of those cases, the Board affirmed the Examiner's decision concerning obviousness. Nine of the 101 cases were directed toward Pharma inventions. Of these, the Board affirmed the Examiner's rejection of the patent claims in 7 cases. Thus, it is apparent that the USPTO itself has raised the bar with respect to obviousness determination, even in the Pharma space.

So what does this all mean? It appears that it is getting tougher to obtain a patent in the first place. The USPTO Examiners now have more ammunition on their side following KSR. Whereas a patent appeal in the past was a decent strategy to obtain a reversal of an obviousness rejection by an Examiner, it is apparent that the Examiners are being upheld at a significantly greater rate than before.

NEW GUIDANCE FOR EXAMINERS

On October 10, 2007, the USPTO issued new Examination guidelines to its Examiners. These guidelines are instructive concerning how Examiners will approach a patent application and how they will ultimately decide its fate concerning obviousness. First, the Examiners are supposed to consider the Graham factors sent forth in the Supreme Court's decision in *Graham v. John Deere Co.*, 86 S.Ct. 684 (1966). The Graham factors are as follows: (1) determining the scope and content of the prior art; (2) ascertaining the differences between the claimed invention and the prior art; and (3) resolving the level of ordinary

BD™ Self-Injection Systems

Bringing you solutions for the home care market

BD

Helping all people live healthy lives

BD Pen II and BD Liquid-Dry Pen

While most patients can use the traditional vial and syringe effectively, it can also prove to be complicated and inaccurate for those who are young, elderly and/or physically/visually impaired[1]. Self-Injection pens are easy to use and help deliver a more precise dosage[2]. BD offers a broad array of self-administration system designs to help meet your product and patient needs.

BD also offers a line of pen needles, which come in a variety of lengths and gauges and are among the thinnest and sharpest needles available on the market.

- Customizable body designs and colors
- Adaptable for liquid or lyophilized drugs
- Reusable and disposable systems
- Adjustable or fixed doses

For more information, please call 800-225-3310 or visit www.bd.com/pharmaceuticals

[1] Graff MR, McClanahan MA. Assessment by patients with diabetes mellitus of two insulin pen delivery systems versus a vial and syringe. Clin Ther. 1998;20(3):486-496.
[2] Weiss, P.M., http://www.femalepatient.com/html/arc/sig/pharma/articles/028_07_031.asp

BD Medical
Pharmaceutical Systems
1 Becton Drive
Franklin Lakes, NJ 07417

BDPS_Marketing@bd.com

skill in the pertinent art. Second, objective evidence relevant to the issue of obviousness must be evaluated by the Examiner as well. Such evidence, sometimes referred to as "secondary factors," include evidence of commercial success, long-felt but unresolved needs, failure of others, and unexpected results.

DETERMINING SCOPE & CONTENT OF PRIOR ART

The Examiners are instructed to perform searches for prior art that cover the claim subject matter and also disclose features that reasonably may be expected to be claimed. They are instructed to search not only in the field of the Applicant's endeavor, but also in fields of endeavor other than that of the Applicant but reasonably pertinent to the particular problem with which the Applicant was concerned. While this was always the case, the likelihood that an obviousness decision will be made using prior art outside of the field of the Applicant's endeavor has become much more likely since the KSR decision.

There are a number of rationales that have been provided to the Examiners to use as a basis for an obviousness rejection. These rationales find their way into the Office Actions issued by the Examiners, interweaved with the actual prior art references being used to reject the claim(s). These rationales are used to support the Examiner's position that:

A. the claim(s) seek to cover a combination of prior art elements according to known methods that yield predictable results;

B. the claim(s) seek to cover a simple substitution of one known element for another to obtain predictable results;

C. the claim(s) seek to cover the use of a known technique used to improve similar devices (methods or products) in the same way;

D. the claim(s) seek to apply a known technique to a known device (method or product) ready for improvement to yield predictable results;

E. the claims seek to cover subject matter that was "obvious to try" — the claims seek to cover a combination chosen from a finite number of identified, predictable solutions, with a reasonable expectation of success;

F. known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations would have been predictable to one of ordinary skill in the art, and this is what the claim(s) seek to cover; and

G. some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention.

For the Examiner to make a rejection using one of the aforementioned rationales (A through F) prior to the KSR decision, the Examiner was also required to provide the rationale set forth in G. In other words, the Examiner needed to show that there was a teaching, suggestion, or motivation within the prior art he relied on to arrive at a rejection based on one or more of rationales A through F. Now, teaching, suggestion, or motivation (the TSM test) to combine different pieces of prior art are not essential for the Examiner to make an obviousness rejection. The rejection can be made without reference to the TSM test. Rather, the TSM test is now just one of many considerations that an Examiner may make to arrive at a decision regarding obviousness. In fact, the "obvious to try" rationale set forth in rationale E was previously used mostly in arguments by patent attorneys against a rejection by the Examiner. "Obvious to try" was previously for the most part considered an improper basis for rejection by the Examiner, when fairly pointed out by a patent attorney as the actual basis for the rejection. A hind-sight analysis that begins with the invention and then seeks to find the components in prior art is considered improper. However, the useful rationales previously mentioned bring the Examiners ever closer to being able to re-create the claimed invention based on the Examiner's new-found knowledge that the invention exists (via the existence of the claim they are examining), without the need to show the basis within that prior art to arrive at the claimed invention. In the past, the Examiner's arguably had to begin their analysis with the prior art and finding a teaching, suggestion, or motivation therein to arrive at the invention.

PHOSITA

One of the Graham factors requires resolving the ordinary skill in the art. To do this, one must determine the skill level of "a person having ordinary skill in the art" or for short, "PHOSITA." A PHOSITA is a hypothetical person who is presumed to have

known the relevant art at the time of the invention.

The determination of a PHOSITA may be made explicitly or implicitly by the Examiner. In any event, this determination may lead to a fertile ground for challenging the Examiner's determination of obviousness. A challenge of an obviousness rejection may be made based upon a disagreement with the Examiner as to what a PHOSITA would actually be capable of doing when encountering the problem solved by the invention. Patentability would be related in part to what types of problems were previously encountered in the art, what types of solutions were raised against such problems, the rapidity in which innovations in the art are made, the sophistication of the technology, and the educational level of the PHOSITA. Such points can be made either by attorney argument in a response to the rejection by the Examiner, alone or in combination with an expert declaration that makes this point. An expert declaration can be made by, for example, the inventor or another colleague of the inventor, or better yet, an independent expert in the filed. It is important to note that the inventor himself is not a person having ordinary skill in the art; rather the inventor is an expert in the field of his/her invention. Therefore, the simple fact that the invention occurred to the inventor doesn't mean it would be obvious to one of ordinary skill in the art.

THERE IS STILL HOPE

While it is indisputable that the standards of patentability at the USPTO have been tightened, all is not lost. In fact, I'm sure that many of you in the past have read a claim of a patent in the Pharma field and scratched your head and wondered how in the world it was ever allowed. These standards will definitely make it harder for a broad-based claim to be allowed without a limitation, which clearly separates the invention from the prior art.

There are a number of things that you can do to improve your chances of obtaining viable patent coverage. First, plan ahead. Research the closest prior art, understand it, and develop one or more themes for the patent application that are set forth in detail therein. The claims should mirror those themes, thereby providing the applicant with arguments against the Examiner's application of rationales A through G in an obviousness rejection.

Second, look at the Examiner's rejection itself. Did the Examiner overstate the level of skill of the PHOSITA? Can this be overcome via attorney argument, perhaps based on other prior art? Should an expert declaration concerning the PHOSITA be presented in addition?

Third, does the Examiner's rejection make sense in of itself? Is it internally consistent? Does the combination preferred by the Examiner for the utility of one or more of the references being combined? Did the Examiner find art that (allegedly) teaches each and every limitation in the claim, or did the Examiner just make an argument concerning some limitations without prior art support?

And, don't forget about the dependent claims. Dependent claims, while often included by inventors and practitioners as "filler," should instead be utilized for the very important purpose of providing additional grounds of patentability. ◆

BIOGRAPHY

Clifford M. Davidson, Esq. is a founding partner at Davidson, Davidson & Kappel, LLC, an Intellectual Property law firm with offices in New York City and Frankfurt, Germany. He counsels pharmaceutical clients in pharmaceutical patent-related matters, including patent prosecution, freedom to operate and infringement opinions, due diligence and tech-transfer, and litigation (including ex parte and inter partes proceedings worldwide). He has assisted specialty pharma and drug development companies to create significant patent portfolios, and the patents he has written and the patent portfolios he has created have been recognized as creating significant value for his clients. He has written patents covering virtually all areas of drug development, and has pioneered strategic patent focus on the pharmacokinetic profiles and the pharmacologic activity of drug/drug formulations. Mr. Davidson earned his BS in Pharmacy and his JD from Rutgers University and is a member of the New York and New Jersey Intellectual Property Law Associations, the American Pharmaceutical Association, and The Controlled Release Society. His area of expertise includes new chemical entities; new pharmaceutical formulations (including controlled-release oral dosage forms, injectables, transdermals, ophthalmics, inhalation, intranasal, sublingual, suppository, and implantation administration); new combinations of previously known drugs; new modes of administration of previously known drugs; method of treatment; pharmaceutical excipients; and methods of preparation.

Investment Trends Driving Combination Product Development

By: Christine M. Ford, MBA

The medical device market is experiencing a surge in venture capital funding like never before. This is due in part to the fact that the medical device arena has room for scale and growth. In addition, because investment levels have been steady and reasonably prudent, there has not been a sense of over-funding in the market like that which has plagued other industries, such as information technology.

As of mid-October, $2.82 billion had already been invested in medical device firms for 2007 compared to the record $2.69 billion in all of 2006.[1] Depending on a final tally for the year, total investments in medical devices in 2007 may have reached $3.75 billion, a more than 40% increase from 2006.[1]

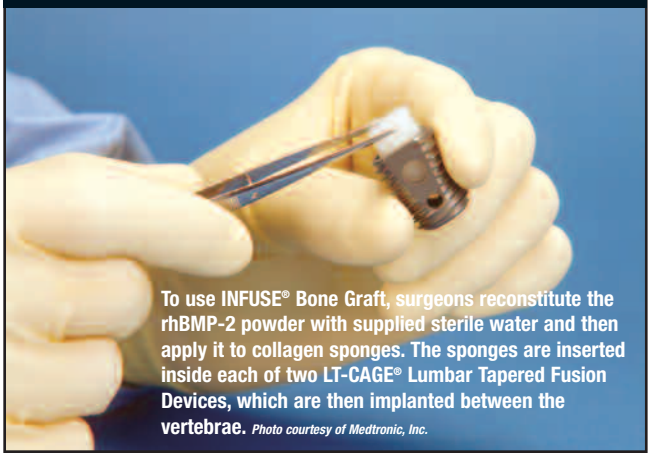
Combination products, which integrate a drug, a biologic, and/or a medical device into a single product, have emerged as an important segment of the well-funded medical device market. This is reinforced by the fact that just about every multi-billion dollar pharmaceutical and medical device company has combination product development plans in their future, according to Veronika Litinski, Director, MaRS Venture Group. Ralph Larson, Chairman and CEO of Johnson & Johnson, echoed this same sentiment when he said "The future is combining devices and drugs."

It comes as no surprise that the majority of companies working on combination products are located near San Francisco and Boston, close to the largest concentrations of venture capital resources. Although these companies are at venture stage and are not yet generating revenue, almost 70% are in the drug-device or drug-biomaterial sector.[2] By contrast, most of the other companies located in these areas are related to information-communication technology.[2]

KEY DRIVERS

Growth of the combination products market is being driven by a number of changes taking place in the healthcare industry today. For one, today's aging American and European populations continue to fuel the medical device boom with their need for innovative, next-generation solutions, which are driving the market in spinal, orthopedic, heart disease, and dermatology among other segments. Rising global healthcare standards and the expiration of patents for blockbuster drugs valued at billions of dollars are also driving the growth of the medical device industry, and specifically combination products.

FIGURE 1



To use INFUSE® Bone Graft, surgeons reconstitute the rhBMP-2 powder with supplied sterile water and then apply it to collagen sponges. The sponges are inserted inside each of two LT-CAGE® Lumbar Tapered Fusion Devices, which are then implanted between the vertebrae. *Photo courtesy of Medtronic, Inc.*

The impact of generic competition on annual sales and the decline in the number of novel drugs reaching the market are creating further demand for combination products. In addition, combination products can also breathe new life into failed pharmaceutical products. For example, a product that exhibited systemic toxicity as a pharmaceutical drug may demonstrate good efficacy locally, making it ideal for use in a targeted drug delivery combination product.

The market size of all convergent/combination products in 2004 was approximately $6 billion and is expected to grow to $10 billion by 2009.[2] It is estimated that almost 90% of this market is related to cardiovascular medicine, of which 80% is drug-eluting stents. The rest of the market comprises orthopedics and other surgical dressing products.[2]

OBSTACLES TO FUNDING

Despite the positive funding environment for medical devices, there are several factors that can make combination products less attractive to venture capitalists. For one, Intellectual Property (IP) becomes more

élan

Let's celebrate success together

by bringing products to market through:

- Product Optimization & Scale-up
- New Product Generation
- Product Rescue

Elan's range of proven technology platform solutions include **NanoCrystal® Technology,** for poorly water soluble compounds, and **Oral Controlled Release Technologies.** These technologies have been used to launch over **30 products worldwide,** with over **US$3B annual in-market sales.**

Together with **scale-up** and **full manufacturing capabilities**, Elan provides you a range of **product enhancement capabilities** to bring products **successfully through to market.**

www.elan.com/EDT

Tel: (U.S.) +1 610 313 7045 (Europe) +353 1 709 4046 E-mail: DrugDelivery@elan.com

complicated when you have multiple parties involved in development - as there are with combination products. As such, patents should be drafted with the goal of protecting developers from the manufacturers who supply the separate components of the combination product. In other words, patents should fully protect all variations of the combination product, not just the final product. For example, if a patent only covers a device combined with a specific biologic, then a competitor might avoid infringement by switching to a different biologic.

Regulatory issues can also present an investment hurdle. Combination products are assigned to one of the three FDA regulatory centers for review - the Center for Biologics Evaluation and Research (CBER), the Center for Drug Evaluation and Research (CDER), or the Center for Devices and Radiological Health (CDRH). However, there are large variations between the three centers in terms of the time and money required to obtain FDA approval. Therefore, a combination product's designation to a particular center can have a big impact on a company's ability to attract financing and to reach its scheduled milestones.

COMBINATION PRODUCTS ON THE INVESTMENT HORIZON

Part of the attraction of combination products is the fact that they can accomplish what neither medical devices nor drugs alone can. While drug-eluting stents have dominated the combination products market up until now, venture firms are looking to invest in more novel innovations, such as those in the areas of tissue engineering, nanomedicine, and spinal fusion.

Regenerative Medicine

The regenerative medicine market is valued at $5 billion worldwide and is expected to reach $10 billion by 2013, making this area of combination product development increasingly attractive to the investment community.[3]

The purpose of regenerative medicine is to help natural healing processes work faster and to re-grow missing or damaged tissue. Regenerative medicine is used to restore function and improve quality of life for patients with multiple sclerosis, cardiac damage, burns, Parkinson's disease, and any condition in which tissue needs to be regenerated. And because regenerative medicine biologically repairs tissue rather than simply preventing further damage, it truly represents a quantum leap forward in medicine. The ability to create replacement livers, spinal cords, the pancreas, hearts, kidneys, and many other tissues and organs would radically decrease hospitalization time, relieve suffering, and prolong life. All of these make a compelling case for investing in this burgeoning area of medicine.

Nanotechnology/Nanomedicine

Nanotechnology is another area witnessing significant investment activity in the combination products arena. According to Lux Research Inc., governments, corporations, and venture capitalists spent $12.4 billion in 2006 on nanotechnology R&D globally, up 13% from 2005.[4] Nanomedicine, the medical application of nanotechnology, represents an important segment of this market.

The applications for nanomedicine range from biomedical imaging to drug delivery to therapeutics. Wyeth Pharmaceuticals' Rapamune® is a great example of nanomedicine within the therapeutics arena. While Rapamune demonstrated great immunosuppressant properties as a traditional pharmaceutical, the drug proved to be toxic in vivo. However, by nanonizing the particles using Elan's NanoCrystal® Technology, the dose was significantly reduced, rendering it efficacious yet non-toxic. Rapamune subsequently went through a new drug approval process at the FDA, followed by successful commercialization by Wyeth, demonstrating its financial viability and medicinal efficacy to the investment community.

Nanomedicine is not limited to pharmaceutical and biological drugs, though. For example, scientists are working to use quantum dots (nanonized semiconductors) to destroy diseased cells in the human body. A classic approach involves coating these quantum dots with antibodies that specifically target and bind to antigens in or on diseased cells. An infrared light is then used to destroy the diseased cells and the quantum dots themselves, which, being of metallic composition, would be harmful if they were to remain in the body. While still in development for nanomedicine applications, quantum dots have already proven effective in forensic investigations.

As a further indication of the investment potential of nanomedicine applications, Freedonia Group, Inc. predicts US demand for nanotechnology-related medical products will increase by more than 17% per year to $53 billion in 2011 and $110 billion in 2016.[5] The greatest short-term impact of nanomedicine is expected to be in therapies and diagnostics for cancer and central nervous system disorders.

Spinal Fusion Technologies

Heart disease may be the leading cause of death in the US, but back pain is the second most common medical condition for which individuals seek treatment, accounting for more than 50 million physician office visits annually in the US.[6] With sales of spinal fixation and dynamic stabilization devices expected to grow at a compound annual rate of 10.4%, reaching more than $3.2 billion in 2012, it is no wonder investors are turning their attention to this segment of the combination products market.[6]

Incidence of spine disorders totaled approximately 75,000 in 2006, and it is estimated that more than 75% of the entire US population will be affected by lower back pain over the course of their lifetime.[6] Not surprisingly, more than $1.8 billion was spent on spinal fixation and dynamic stabilization devices in the US in 2006.[6]

Combination spinal fusion devices that use Bone Morphogenic Protein (BMP) enable degenerative disc disease to be treated in a single surgery. Until now, spinal fusion procedures actually required two surgeries — one to harvest pieces of bone from the patient's hip (autograft) and a second to implant them into the spine. The two-surgery approach required pieces of bone to be chipped off the patient's hip in a painful surgical procedure. According to numerous studies, the harvesting procedure is actually more painful than the fusion itself, and nearly one-third of patients experience hip pain for up to 2 years following surgery. The new BMP approach also enables patients to undergo spinal fusions without the morbidities associated with secondary surgeries.

One example of this revolutionary technology is Medtronic's INFUSE® Bone Graft and the LT-CAGE® Lumbar Tapered Fusion Device (Figure 1), which is used in combination to treat degenerative disc disease. INFUSE Bone Graft contains a genetically engineered version of a protein that occurs naturally. The resulting recombinant human protein is known as rhBMP-2, and when combined with an absorbable collagen sponge, is marketed by Medtronic Sofamor Danek under the tradename INFUSE Bone Graft.

Combination spinal fusion devices continue to be approved for new indications, demonstrating that the potential of this market is far from exhausted.

THE FUTURE IS CONVERGENCE

Like any new innovation of the past half century, combination products will pass through a maturity curve. However, the benefits of combination products far outweigh the engineering, scientific, regulatory, and business challenges associated with bringing them to market.

The potential to introduce new innovations that transcend the life-saving and life-enhancing abilities of traditional pharmaceuticals or medical devices will keep investment strong in this segment. This investment is also indicative of the ubiquitous role combination products are poised to play in the medical device arena. ◆

REFERENCES

1. Austin S. The week in venture capital, healthy investments in medical device companies. Market Watch from Dow Jones, Oct. 27, 2007.
2. Shmulewitz A, Langer R. The ascendance of combination products. Nature Biotechnol. 2006;24:277-280.
3. Tissue Engineering & Stem Cell Technology Report 2007, Visiongain, February 2007.
4. Reisch M. Nano goes big time. Chem & Engin News. Jan. 22, 2007.
5. Nanotechnology in Healthcare. The Freedonia Group, Inc., Cleveland, OH; 2007.
6. Medtech Insight, U.S. Spinal Surgery Markets: Advances in Spinal Fusion and Dynamic Stabilization Products. March 2007, 179 pages, Report #A308.

BIOGRAPHY

Ms. Christine M. Ford is Event Director of PharmaMedDevice (www.pharmameddevice.com). Since joining Reed Exhibitions in 1991, she has been involved in a variety of conference and event management positions within a range of event portfolios, including technology, life sciences, and manufacturing. Ms. Ford served as Reed Exhibitions' Director of Business Development from 2000-2005, working on a variety of launch and acquisition projects. Since 2004, she has focused the majority of her business development work within the life sciences and healthcare industries, including the PharmaMedDevice launch. She earned her MBA from the University of Connecticut and her BS from Fairfield University. She can be reached at (203) 840-5391 or cford@reedexpo.com.

INJECTABLE PACKAGING

A Historical Look at Injectable Pharmaceutical Packaging

By: Frances L. DeGrazio

INTRODUCTION

Throughout the years, there has been very little change in the appearance of components in packaging and delivery systems for injectable drug products. The material science and manufacturing technologies that go into the creation of these systems, on the other hand, have undergone significant advancement. This article will review the drivers behind these changes as well as cover what can be expected moving forward, including the industry's requirements for ultra-clean, ultra-high-quality packaging and administration systems and system components; the impact of regulatory guidances driving an industry need for risk mitigation; the impact of advanced technologies for pharmaceutical manufacturing; and the shift in healthcare delivery to the increasing use of self-administered drugs.

THE DRIVE FOR QUALITY & CLEANLINESS

The most notable change to pharmaceutical packaging and packaging components has been the increasing emphasis on closure cleanliness. Pharmaceutical manufacturers must ensure the purity of their drugs and provide products that are safe for the patients and for those administering the drug. To achieve these standards, manufacturers are specifying packaging systems and components that eliminate, as much as possible, the risk to their drugs caused by particulate, processing aides, and extractables and leachables.

This emphasis on cleanliness has been driven by, among other factors, the emergence of biopharmaceuticals and is taking hold in the industry in general. That's not to say that the industry was not quality-focused years ago. On the contrary, the industry turns on its reputation for product purity. Over the years, however, standards for packaging systems and components have evolved to meet the requirements for containing and delivering increasingly sophisticated drug products. Just as pharmaceutical product development and

FIGURE 1

West Spectra Seals™ Sophisticated electronic vision inspection systems are required for today's packaging components.

FIGURE 2

Westar RS® Components
Today, component manufacturing and packaging in classified areas and clean rooms (up to Class 100 [ISO 5]) is commonplace.

manufacturing have come a long way, so, too, have delivery systems and components.

Today, component manufacturing in classified areas and clean rooms (up to Class 100 [ISO 5]) is commonplace; more than a quarter century ago, manufacturing proceeded in environments that, in the pharmaceutical sense, were far from clean. In addition, component manufacturers operate in a cGMP environment; back then, adherence to cGMPs was not required. Currently, ultra-high quality is achieved with systems such as sophisticated electronic vision inspection. In 1970, quality was highly dependent upon the vision of plant employees.

The difference in component manufacturing compared to now and then is astounding to those who are not familiar with the processes. Although the manufacturing processes from the two eras appear nearly identical, the technologies and systems behind the processes are radically different.

Today's elastomer manufacturing facility is extremely high-tech. From the receipt of raw materials to the shipping of final products, every step is documented and measured to ensure traceability. These procedures are in place to ensure a high-quality product is delivered. Quality encompasses everything from traceability throughout the manufacturing process through the collection of in-process data and the improved cleanliness of the final product.

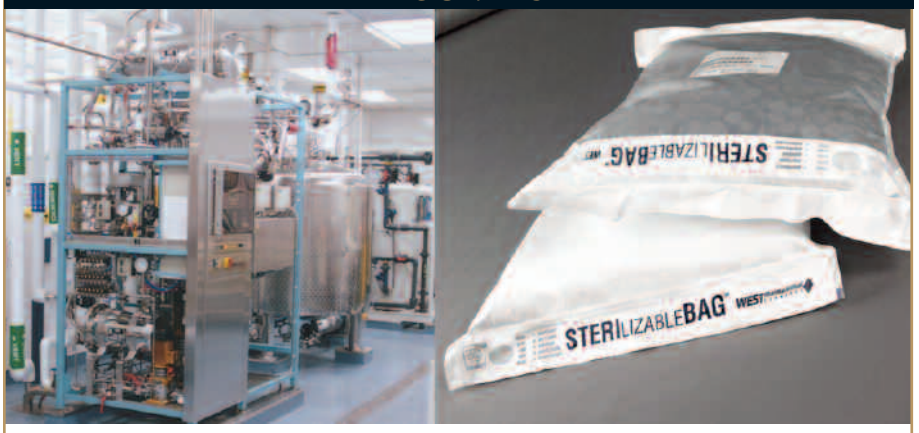
A visitor to a plant in 1970 would find an operation that bore scant resemblance to a pharmaceutical manufacturing facility of today. Thirty years ago, primary packaging components – that is, components like stoppers and syringe plungers that contact the packaged drug – were manufactured from elastomeric materials, many of which contained dry natural rubber. The manufacturing process consisted of blending the raw materials to form a sheet of rubber. The individual parts were formed by compression molding. A molded sheet could have hundreds or even thousands of individual parts that were trimmed in a die press. Some trimmed parts were washed, while others were packed in plastic bags for shipping to the customer.

The components were frequently treated with silicone oil as a means of overcoming the tackiness inherent in an elastomeric product. Without some form of lubrication, the components would not process in a pharmaceutical filling line. Silicone oil, however, can transfer from the closure to the drug product.

To reduce reliance on silicone oil, component manufacturers developed films and coatings that provided lubricity for filling line performance and provided a barrier against extractables. In the 1970s, a fluorinated ethylene-propylene (FEP) coating was applied to the drug contact side of serum stoppers, providing both a barrier and lubricity. The film adheres readily to the flat surface of a serum stopper or syringe plunger, but cannot be applied to the more complex geometric shapes of lyophilization stoppers.

To solve this problem, component manufacturers utilized films made from other fluorocarbon materials. These materials are conformable and provide

FIGURE 3



WFI Processing Equipment
Today, pharmaceutical packaging components are washed in Water For Injection, and final packing is done in a Class 100 clean room. The bags used to pack the washed components are suitable for direct entry into a sterilizer.

FIGURE 4

West Pharmaceutical Services, Inc.

The molded sheet of elastomer components moves from molding to trimming. Thirty years ago, portions of the trimming operation were done by hand. Modern trimming dies operate at a high level of precision. The result is a component with very little deviation from the standard.

excellent barrier protection. Further, fluoro-elastomer films have superior lubricity properties.

Another option for enhancing component performance on filling lines is a cross-linkable siloxane-based coating that is cured on the surface of elastomer components by ultraviolet light. This type of coating provides lubricity, but does not have barrier properties.

Stoppers and syringe plungers are not the only primary packaging components undergoing change. Many new drugs, especially those used for oncology, are sensitive to the glass used for vials and syringe barrels. Contaminants from the glass can leach into the drug product and, in some instances, can be worth thousands of dollars per dose. This new generation of high-value, life-saving biopharmaceutical therapies requires equally high-value packaging and administration systems to maintain the drug's biological integrity and to maximize its therapeutic benefits.

Some manufacturers are switching their products from glass vials and syringe barrels to products manufactured from cyclic olefin copolymers (COC) and cyclic olefin polymer (COP) materials. These resins are inert and have many ideal properties, such as extremely low extractables, high heat resistance, excellent low temperature characteristics, excellent drainability, and low moisture permeability that are favorable for high-potency, high-value drugs.

A DELIBERATE EVOLUTIONARY PROCESS

The high standard of quality and cleanliness within the pharmaceutical packaging environment came as no mistake; rather it was a deliberate decision to create a cGMP environment. From the manufacturing floor and into a company's day-to-day operating procedures, cGMP represented a huge shift in thinking. It required improved traceability of the raw materials chain; introducing new systems for quality control and quality assurance testing of raw materials, work-in-progress and finished goods; and tightening manufacturing and operating procedures and product specifications to achieve new levels of quality.

Today's packaging plant resembles a pharmaceutical manufacturing facility; the level of quality and cleanliness are set to the same high standards for both. Employees in manufacturing and processing areas wear protective clothing appropriate for the work space's classified environment to keep particulate and fibers out of the manufacturing area. They are trained thoroughly on cGMP requirements.

The quest for quality begins even before raw materials are received at the plant. Materials are purchased based on the suppliers' ability to meet tight tolerances and strict quality standards.

Incoming raw materials are sampled and tested; the lots are not released for production until the lab determines that specifications are met. Today's elastomeric formulations are blended from fewer materials that are less extractable. The formulations used many years ago would not be acceptable for new drug products today because of extractable and leachables concerns and because some of the materials used in the 1970s would not meet today's industry guidelines. In addition, the properties of today's elastomers help pharmaceutical manufacturers meet shelf-life requirements and provide better performance during administration, such as coring and resealing properties. Further, today's elastomers have helped to improve the manufacturing process. As a result, molding yields fewer rejected parts.

The mixing equipment used to blend the ingredients that go into the

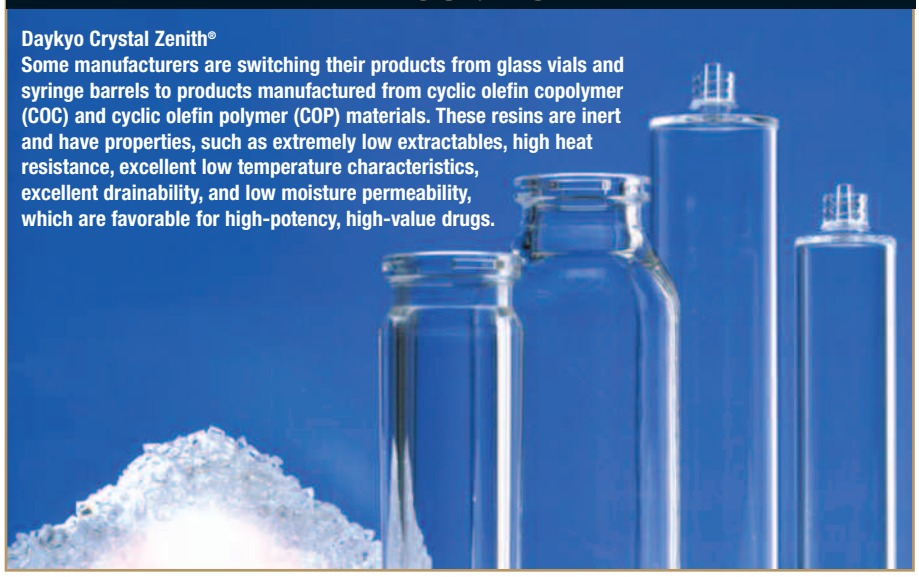
elastomeric formulations is closed to keep outside contaminants to a minimum. The calendaring and extrusion processes are able to achieve the tightest of dimensional tolerances for the sheeting that will be used to mold the components. Improved equipment and quality systems, such as in-process metal detectors, help ensure the highest quality finished components.

The molded sheet of components moves from molding to trimming, where a die trims the individual parts from the sheet. Today's trim dies operate at a high level of precision. The result is a component with very little dimensional deviation from the standard and fewer instances of particulate from the trimming process.

Post-manufacturing processes have also advanced significantly. In today's manufacturing environment, downstream processing frequently includes washing in a pharmaceutical-grade washer to yield components that are shipped to manufacturers ready-to-sterilize. The final rinse uses Water For Injection, and final packing is done in a Class 100 clean room. The bags used to pack the washed components are suitable for direct entry into a sterilizer.

The contrast to 1970s processing is striking. Three decades ago, most components were trimmed and dropped into a poly bag. The bag was secured with a twist tie and shipped to the customer in a corrugated box. Component washing was rudimentary compared with today's process; the wash did little more than remove lubricants applied during the trimming operation.

FIGURE 5



Daykyo Crystal Zenith®
Some manufacturers are switching their products from glass vials and syringe barrels to products manufactured from cyclic olefin copolymer (COC) and cyclic olefin polymer (COP) materials. These resins are inert and have properties, such as extremely low extractables, high heat resistance, excellent low temperature characteristics, excellent drainability, and low moisture permeability, which are favorable for high-potency, high-value drugs.

THE IMPACT OF REGULATORY GUIDANCES

Guidances issued by the US FDA have had a strong impact on the drive to cleanliness and ultra-high quality. In 1999, the FDA released the Guidance for Industry – Container Closure Systems for Packaging Human Drugs and Biologics. This container closure guidance created a fundamental shift in the relationship between pharmaceutical manufacturers and their suppliers. The Guidance for Industry – Sterile Drug Products Produced by Aseptic Processing, September 2004, was intended to help pharmaceutical companies meet cGMP regulations when manufacturing sterile drug and biologic products using aseptic processes.

These guidances defined the FDA's thinking on issues related to primary packaging and administration system components and added to the pressure on pharmaceutical manufacturers to manage their filling line risks. As regulatory requirements for packaging components have changed, pharmaceutical manufacturers have become more vulnerable to FDA inspections and, if violations are found, to actions that could impact their manufacturing operation.

The development of barrier isolation technology, while initiated nearly 20 years ago, finally began to take hold in the early 1990s. Isolator technology requires packaging components clean enough to be introduced directly into the isolator unit.

Beginning in the 1990s, pharmaceutical manufacturers had the option to mitigate some of the component preparation risks by buying components that were ready-to-use (RU) or ready-to-sterilize (RS). This option, in addition to helping mitigate risk, also helped streamline their operations by eliminating the component preparation steps. However, the impact on the component manufacturer was dynamic. Processing RS and RU products required clean room facilities for washing and final packing, the addition

FIGURE 6

West Pharmaceutical Services, Inc.

Component Processing in 1952 | Component Processing in 2007

The molded sheet of elastomer components moves from molding to trimming. Thirty years ago, portions of the trimming operation were done by hand. Modern trimming dies operate at a high level of precision. The result is a component with very little deviation from the standard.

of sterilization equipment, and the development of expertise and knowledge of microbiological testing.

Those carefully prepared components are now shipping in plastic boxes loaded on plastic pallets. It is necessary to eliminate corrugated boxes and wood pallets because of their potential source of particulate and contamination. Now, ready-to-use components are just entering the market – a product with these characteristics would have been unimaginable three decades ago.

A CHANGING PHARMACEUTICAL INDUSTRY

Changes in pharmaceutical industry research and manufacturing technologies have driven significant developments in packaging and delivery systems. The increase in the number of large-molecule, biopharmaceutical drugs in development pipelines has increased the need for injectable packaging and administration systems. The old glass and elastomer closure systems may not provide the effective barrier properties needed for high-value, life-saving therapies. Component manufacturers have responded with new materials and technologies that ensure extended drug product shelf-life.

Many of the new biotechnology-derived drug therapies are unstable in liquid form, and as a result, are introduced as lyophilized or dry powder dosage forms. Lyophilized drugs need special stoppers for optimal performance in lyophilization chambers. The stoppers must solve a problem of the stopper sticking to the lyophilization shelf after the cycle is completed. In addition, lyophilized drugs typically are reconstituted at the point-of-care, thus requiring "patient friendly" administration systems.

THE RISE OF SELF-ADMINISTRATION

Throughout the years, there has been a shift from hospital care to home care. In 1970, healthcare revolved around hospital care. Today, because of cost constraints and the introduction of maintenance-type drugs for treating chronic conditions, such as arthritis, cancer, multiple sclerosis, and other diseases that require frequent medication, healthcare revolves around the home. Many of the maintenance therapies are delivered by injection, driving a need for patient-friendly administrations systems. These systems have to ensure the potency of the drug, be tamper evident, help deter counterfeiting, promote compliance with a dosing regimen, ensure dosing accuracy, be safe and easy to use, and be as pain-free as possible.

An outgrowth of these changes is the move from the typical vial and disposable syringe to a prefillable syringe. With prefillables, dosing accuracy is ensured. However, prefillables present some challenges for the industry. For the pharmaceutical company, the need is for a prefillable system that protects the integrity of the packaged drug product over time and will function as represented over the full shelf-life of the drug product. The response from component manufactures was the development of syringe plungers with barrier films that minimize the interaction between the packaged drug and the components. At the same time, they have developed elastomers for molded plungers that maintain functional properties, such as seal integrity and breakloose and extrusion forces.

When self-administered drugs are in lyophilized or dry powder form, manufacturers must find methods or packaging systems that help prevent accidental needle-stick injuries, incomplete mixing, inaccurate dosing, and drug spray-back. Manufacturers familiar with the drug administration process need to provide delivery systems that will simplify drug reconstitution, especially for non-professional care givers.

LOOKING FORWARD

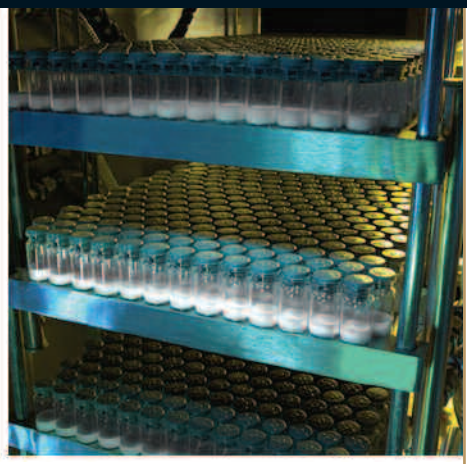
Packaging and delivery systems as a differentiator for drug products will continue to become more important, especially in crowded therapeutic areas and for solving industry-wide problems, such as drug product counterfeiting. The market today is receptive to packaging systems that can provide track-and-trace capabilities and product authentication throughout the supply chain. Pharmaceutical seals are an ideal platform for these technologies. We can expect to see wider use of technologies, such as radio frequency identification (RFID) tags embedded in the plastic button affixed to the seal or ultraviolet inks applied to the seal. RFID has the potential to provide item-level security that can help secure the supply chain.

The drive for cleanliness and purity will no doubt continue into the foreseeable future. With advances in material science, we can expect cleaner elastomeric formulations for manufacturing primary packaging and delivery system components. We can also expect coatings with near-total barrier properties. Processing aides, such as silicone oil, will be eliminated, and quality levels will approach a zero-defects standard.

As the great Yankee, Yogi Berra, said, "it's tough to make predictions, especially about the future." But we, as package component and drug administration system manufacturers, can make one prediction with confidence. As pharmaceutical research continues to develop advanced, life-saving therapies, the systems used to package and administer those therapies will keep pace through advances in material science and innovative design.

FIGURE 7

West Pharmaceutical Services, Inc.



Lyophilzation stopper with a fluorocarbon coating to provide low-surface-energy characteristics that prevent sticking in the lyophilzation chamber.

Lyophilzation chamber at the end of a cycle.

Many of the new biotechnology-derived drug therapies are unstable in liquid form, and as a result, are introduced as lyophilized or dry powder dosage forms. Lyophilized drugs need special stoppers for optimal performance in lyophilization chambers. The stoppers must solve a problem of the stopper sticking to the lyophilization shelf after the cycle is completed. In addition, lyophilized drugs typically are reconstituted at the point-of-care, thus requiring "patient friendly" administration systems.

BIOGRAPHY

Ms. Frances L. DeGrazio entered the industry in 1983 working for 6 months at Pierce and Stevens Chemical Corporation before joining West. She has been with West ever since. Throughout her tenure at West, she has served in various functions with the analytical laboratory and research and development areas. Thirteen years were spent in the area of Customer Technical Support, with her last position being Vice President of Global Technical Support and Contract Laboratory Services with responsibilities for both strategic planning and implementation for both organizations. She was promoted to Vice President, Quality Assurance, Americas, in 2002 with responsibility for quality assurance and quality control for nine manufacturing facilities and the corporate analytical laboratories. In 2004, she assumed direction for the Regulatory group as well. In May 2006, she transitioned into her current role as Vice President of Marketing and Strategic Business Development. She is a member of the Parenteral Drug Association (PDA), American Chemical Society (ACS), and the American Association of Pharmaceutical Scientists (AAPS). Ms. DeGrazio earned her BS in Chemistry from Cabrini College in Radnor, Pennsylvania.

NANOMEDICINE

The Upcoming Era of Nanomedicine: A Briefing

By: Bhupendra.G.Prajapati, MPharm; Jayvadan K. Patel, PhD; Vishnu M. Patel, PhD; and Krunal V. Prajapati

INTRODUCTION

An increasingly diverse library of devices and technologies are used to aid drug targeting and delivery. The technologies include natural vectors (antibody and protein carriers, recombinant proteins, liposomes, and viruses), pseudo-synthetic vectors (polymercoated liposomes, polymer-antibody hybrids), and synthetic vectors (polymer conjugates, polymeric micelles, and nanoparticles). The concepts of antibody-conjugates, liposomes, nanoparticles, and polymer-conjugates were born in the 1970s.

Nanomedicine is beginning to emerge from research in nanotechnology. Nanotechnology refers to the manipulation of single atoms via the structural control of matter at the molecular level. Nanotechnology is working on a scale of 1 billionth of a meter to yield nanodevices such as mini machines and nanomaterias.

Looking to the nanosize range, "nanomedicine" can be best defined as the science and technology of diagnosing, treating, and preventing disease and traumatic injury; relieving pain; and preserving and improving human health, using molecular tools and molecular knowledge of the human body. Nanomedicine can also be defined as the application of atom manipulation to the preclusion and hopeful treatment of diseases that can otherwise infect the human body. Lastly, nanomedicine has been described as medical treatment at the level of single molecules or molecular assemblies that provide structure, control, signaling, homeostasis, and motility in cells (ie, at the "nano" scale of about 100 nm or less).[1]

FIGURE 1

The respirocyte was conceived and designed by Robert A. Freitas Jr. In this image, four respirocytes tumble through space at various orientations. Pumping station geometry and polar barcodes are clearly visible. Reprinted with permission from Forrest Bishop (artist) and Robert A. Freitas, Jr.

APPLICATIONS OF NANOMEDICINE

Nanomedicine has applications for analytical techniques and diagnostic tools, nano-imaging and manipulations, nanomaterials and nanodevices, the design of biologically active therapeutics or drug delivery systems, and all issues relating to their pharmaceutical development and clinical use with particular regard to potential toxicity. Specifically, nanomedicine can be used:

1. To improve antimicrobial properties and to investigate nanomaterials with strong antimicrobial properties. Nanocrystalline silver, for example, is already being used for wound treatment.[2,3]

2. In biopharmaceutics, specially for drug delivery applications using nanomaterial coatings to encapsulate drugs and to serve as functional carriers. Drug encapsulation materials include liposomes and polymers, ie, polylactide (PLA) and lactide-co-glycolide (PLGA), which are used as microscale particles. The materials form capsules around the drugs and permit timed drug release to occur as the drug diffuses through the encapsulation material. The drugs can also be released as the encapsulation material degrades or erodes in the body. Nanomaterial encapsulation could improve the diffusion, degradation, and targeting of a drug as it has a larger surface area for the same volume, smaller pore size, improved solubility, and different structural properties.[4-6] More sophisticated nanomedical devices may carry specific drugs, that are targeted at certain "damaged" cells, such as which those that are cancerous. Nanomaterials could serve as camouflage to avoid immune responses

ONE STOP

service for product development & licensing decisions

www.pharmacircle.com

The Only Knowledge Management Service integrating complete drug delivery information into the broader analysis of the Pharma/Biotech Pipeline, Products and Deals

- Complete, comprehensive and up-to-date drug delivery information and analysis for better product decisions
- Detailed scientific and business related information on Pharma/Biotech, Drug Delivery, Specialty Pharma companies, including technologies, pipeline & products acquisitions & deals to facilitate licensing and competitive intelligence efforts
- Interactive and powerful search engine with user customized filters displays strategic information & analysis just the way you want to see them
- Web based service also provides phone & e-mail support

new

Please visit our free contract pharma section which provides detailed listings and comparison of services

For more Information please visit, www.PharmaCircle.com or contact tkararli@pharmacircle.com at (847) 729 2960

or as agents that could catalyze or respond to certain molecules or chemical events. Nanoparticle encapsulation is also being investigated for the treatment of neurological disorders to deliver therapeutic molecules directly to the central nervous system beyond the blood-brain barrier, and to the eye beyond the blood-retina barrier. Applications could include Parkinson's, Huntington's, Alzheimer's, ALS, and diseases of the eye. Neurotech for ophthalmic disorders represent a rapidly growing area that can treat various diseases, such as age related macular degeneration (AMD), diabetic retinopathy, glaucoma, and retinitis pigmentosa (RP).[7]

3. To improve implantable materials using nanomaterials for tissue repair and replacement of damaged or diseased tissues, eg, stem cells. Hard tissues such as bone and teeth can be made more compatible at the time of replacement by coating them with a biocompatible material to increase their adherence properties and produce a greater surface area-to-volume ratio for the highest possible contact area between the implant and natural tissue. This can improve the lifespan of implants and provide a framework (via nanostructure scaffolds) for improved tissue regeneration. Moreover, nanomaterial implants could be engineered for biocompatibility with the host environment to minimize side effects and the risk of rejection. Smart nanomaterials could detect and respond to environmental conditions and chemical reactions.

4. As diagnostic tools, in vivo "labs on a chip" employ nanotech biosensors and microfluidics to continuously monitor body temperature, pulse, heart rhythm, blood pressure and flow, oxygenation, or glucose plane; work multiple DNA tests; detect pathogens or toxins; or diagnose cancerous tumors while they are very tiny.[9]

5. Nanotechnology can now offer new implantable and/or wearable sensing technologies that provide continuous and extremely accurate medical information. Complementary microprocessors and miniature devices can be incorporated with sensors to diagnose disease, transmit information, and administer treatment automatically if required. These kinds of implantable small devices can serve as sensors in fluid injection systems, drug dispensers, pumps, and reservoirs and aid in restoring vision and hearing functions. Devices with nanoscale components could monitor environmental conditions (temperature and pH), detect specific properties, and deliver appropriate physical, chemical, or pharmaceutical responses (eg, polyethylene glycol beads coated with fluorescent molecules to monitor diabetes blood sugar levels). Another type of implantable sensor uses MEMS (micro electromechanical system) devices and accelerometers for monitoring and treating paralyzed limbs. Implantable MEMS sensors can measure strain, acceleration, angular rate, and related parameters to determine normal and problem data. In the longer term, the development of nanoelectronic systems that can detect and process information could lead to nanodevices that serve as retina implants by acting as photoreceptors as well as cochlear implants by improving nerve stimulation.[8] An advancement in nanotechnology that may allow us to build artificial red blood cells called respirocytes capable of carrying out the functions of natural blood cells already exists.

RESPIROCYTES

Artificial red blood cells or respirocytes are blood borne spherical 1-micron diamondoid 1000-atm pressure vessels with active pumping powered by endogenous serum glucose, able to deliver 236 times more oxygen to the tissues per unit volume than natural red cells and to manage carbonic acidity. An onboard nanocomputer and numerous chemical and pressure sensors enable complex device behaviors remotely reprogrammable by the physician via externally applied acoustic signals. Primary applications will include transfusable blood substitution; partial treatment for anemia, perinatal/neonatal, and lung disorders; enhancement of cardiovascular/neurovascular procedures, tumor therapies, and diagnostics; prevention of asphyxia; artificial breathing; and a variety of sports, veterinary, battlefield, and other uses.[10]

Each respirocyte is able to detect the concentration of gases in the blood by using sensors over the surface. Gas molecules can enter the tanks inside the respirocyte via molecular sorting rotors. These rotors have pockets that can spin and pick up and drop off oxygen and carbon dioxide molecules.

CANCER TREATMENT

Current research is proceeding in two main ways. One is laboratory-based diagnostics, and the second is in vivo diagnostics and treatment. In vivo nanostructures could carry and deliver large amounts of anti-cancer drugs into cancerous cells without harming the healthy cells, reducing the side effects related to current cancer therapies. This means the drug will be able to target only the cancerous cells.

Dendrimers have the potential to detect, diagnose, and treat cancer. The branching shape of dendrimers can also be used for the attachment of drugs because it can provide a large surface area. Dendrimers are synthetic spherical polymers (1 to 10 nm in size) of uniform molecular weight made from branched monomers. Dendrimers act as nanoscale platforms on which molecules with different functions can be attached. A single dendrimer can carry a molecule that recognizes cancer cells, a therapeutic agent to kill those cells, and a molecule that recognizes the signals of cell death.[11-14] Researchers hope to manipulate dendrimers to release their contents only in the presence of certain trigger molecules associated with cancer. Following drug release, the dendrimers may also report back whether

they have successfully killed their targets.

Fullerenes (or Buckyballs) are natural hollow spheres (1 nm in diameter) made up of 60 carbon atoms.[15] Fullerenes create a unique drug delivery platform that enable active pharmacopheres to be grafted to their surface in three-dimensional orientations for precise control in matching fullerene compounds to biological targets, entrapping atoms within the fullerene cage, and attaching fullerene derivatives to targeting sites. C Sixty is developing fullerene-based drug delivery platforms that link fullerenes with antibodies and other targeting agents. Some of C Sixty`s drug delivery systems include fullerene-decorated chemotherapeutic constructs, fullerene-radiopharmaceuticals, and fullerene-based liposome systems (called Buckysomes) for the delivery of single drug loads or multiple drug cocktails. Employing rational drug design, C Sixty has produced several drug candidates using its fullerene platform technology in the areas of HIV/AIDS, neurodegenerative disorders, and cancer.

A layered sphere called a nanoshell is being developed by Nanospectra for drug delivery.[16] The nanoshell has a gold exterior layer that covers interior layers of silica and drugs. Nanoshells can be made to absorb light energy and then convert it to heat. As a result, when nanoshells are placed next to a target area such as tumor cell, it can release tumor-specific antibodies when infrared light is administered.

DANGERS OF NANOMEDICINE

Imagination raises the question of out-of-control nanomachines that could replicate themselves and consume everything in their path as they reproduce and multiply. For this to occur, however, a self-replicating assembler would need to have a molecular structure and the correct diet for replication within “arms reach,” which is unlikely. Such a machine would also need artificial intelligence to survive. Humans would also need to install this intelligence; therefore, the grey goo would have to be capable of its own evolution to be a threat.

REFERENCES

1. National Institutes of Health. NIH roadmap for nanomedicine. Bethesda,MD:NIH;2004.
2. Bhol KC, Schechter PJ. Topical nanocrystalline silver cream suppresses inflammatory cytokines and induces apoptosis of inflammatory cells in a murine model of allergic contact dermatitis. Br J Dermatol. 2005;152(6):1235-1242.
3. Website referenced: www.burnsurgery.org/Modules/nano/p2/p2title.htm.
4. Perugini P, Simeoni S, Scalia S, Genta I, Modena T, Conti B, Pavanetto F. Effect of nanoparticle encapsulation on the photostability of the sunscreen agent, 2-ethylhexyl-p-methoxycinnamate. Int J Pharm. 2002;246(1-2):37-45.
5. Radwan MA, Aboul-Enein HY. In vitro release and stereoselective disposition of flurbiprofen loaded to poly(D,L-lactide-co-glycolide) nanoparticles in rats. Chirality. 2004;16(2):119-125.
6. Qaddoumi MG, Ueda H, Yang J, Davda J, Labhasetwar V, Lee VH. The characteristics and mechanisms of uptake of PLGA nanoparticles in rabbit conjunctival epithelial cell layers. Pharm Res. 2004;21(4):641-648.
7. Website referenced: www.neurotech.fr/product_tech.asp.
8. Website referenced: www.cs.washington.edu/mssi/tic/intros/Bohringer.
9. Website referenced: www.nanoimplants.com.
10. Website referenced: www.foresight.org/Nanomedicine/Respirocytes.html.
11. Sampathkumar SG, Yarema KJ. Targeting cancer cells with dendrimers. Chem Biol. 2005;12(1):5-6.
12. Choi Y, Baker JR, Jr. Targeting cancer cells with DNA-assembled dendrimers: A mix and match strategy for cancer. Cell Cycle. 2005;4(5):669-671.
13. Website referenced: http://drugresearcher.com/news/news-ng.asp?n=60671-dendrimers-deliver-cancer.
14. Website referenced: http://newscenter.cancer.gov/cancertopics/understandingcancer/nanodevices/Slide22.
15. Website referenced: http://www.mindspring.com/~kimall/Fuller/fullerenes.html.
16. O'Neal DP, Hirsch LR, Halas NJ, Payne JD, West JL. Photo-thermal tumor ablation in mice using near infrared-absorbing nanoparticles. Cancer Lett. 2004;25;209(2):171-176.

BIOGRAPHIES

Bhupendra G. Prajapati is an Assistant Professor in the Department of Pharmaceutics and Pharmaceutical Technology at S.K. Patel College of Pharmaceutical Education and Research, Ganpat University, Kherva-382711, Gujarat, India. He can be reached at bhupendra.prajapati@ganpatuniversity.ac.in.

Dr. Jayvadan K. Patel is an Associated Professor and Head of the Department of Pharmaceutics and Pharmaceutical Technology at S.K. Patel College of Pharmaceutical Education and Research, Ganpat University, Kherva-382711, Gujarat, India. He can be reached at jayvadan04@yahoo.com.

Dr. Vishnu M. Patel is an Assistant Professor in the Department of Pharmaceutics and Pharmaceutical Technology, APMC College of Pharmaceutical Education and Research, North Gujarat University, Himattnagar, Gujarat, India.

Krunal V. Prajapati is post-graduate student in Pharmaceutical Science at Greenwich University, United Kingdom.

DRUG DELIVERY Executive

PharmaForm™ LLC
Excellence & Innovation in the Pharmaceutical Sciences

PharmaForm, LLC: Drug Delivery & Product Development Expertise

Michael Crowley, PhD
Vice President, Business Development
PharmaForm

"We are finding more and more that client companies are looking for external resources to help them find a better solution, faster. It often isn't just a question of sourcing additional expertise, it is also a question of getting more hands to move the project to the next milestone more quickly."

PharmaForm, LLC is a pharmaceutical contract service organization with a national and international reputation for delivering novel and innovative solutions to challenging problems in pharmaceutical product development, manufacturing, and analytical services. In addition, the Austin, Texas-based company offers private-label and contract packaging, blending, and filling services. PharmaForm has worked with client groups varying from emerging virtual companies to the largest pharmaceutical companies in the world. Its products are made under the supervision of the highest quality systems in abidance with FDA regulations, taking great pride in its ability to provide exceptional service to each customer group by listening to and responding to the individualized needs of the client. Drug Delivery Technology recently interviewed Michael Crowley, PhD, Vice President, Business Development of PharmaForm, to learn more about his perspectives on providing services to the pharmaceutical and biotechnology industries.

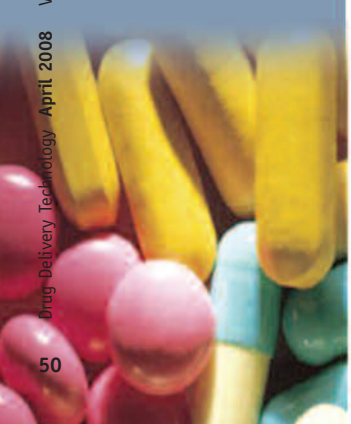
Q: Can you provide a brief overview of PharmaForm's services and technologies for our readers?

A: As a pharmaceutical contract service provider, PharmaForm offers a wide range of formulation, product and process development, GMP manufacturing, analytical testing, and patent litigation support services. We have helped clients develop products meeting important clinical challenges using oral, nasal, pulmonary, dermal, mucosal, and vaginal delivery. Beyond formulation, we offer our clients GMP manufacturing and analytical services throughout the development process from the preclinical to commercial stages.

Many clients have come to us for patent litigation support. The services we provide in this area include case evaluation, analytical characterization, critical data review and interpretation, as well as trial preparation. When it comes to trial support, we provide assistance through expert deposition and testimony. Our scientific team is recognized as drug delivery experts, and we have successfully assisted our clients in defending several pharmaceutical products.

Q: What are PharmaForm's core areas of expertise?

A: PharmaForm is renowned for its expertise in Hot-Melt Extrusion. Our scientists have published about 45 peer-reviewed publications on this topic and have developed significant intellectual property. We have R&D and GMP hot-melt extrusion equipment that supports product and process development as well as small commercial-scale manufacturing. We have expertise in developing low-dose, high-potency



oral dosage forms. PharmaForm has developed tablet formulations with doses ranging from 500 micrograms to as low as 50 nanograms that meet USP content uniformity requirements. Our facility and GMP suites were designed to work with potent and scheduled compounds, including many SafeBridge class III compounds. We are DEA registered and licensed, with the necessary infrastructure to support handling and inventorying of scheduled products.

In the area of formulation, our scientific team has core expertise and experience in improving the solubility of poorly soluble compounds. Our clients have been very pleased with formulation enhancements that have led to significant improvements in clinical bioavailability. We have considerable experience with bioadhesive systems and the targeting of drug delivery along the GI tract. One client recently received marketing approval for its drug product in a pulsatile-release system developed at PharmaForm.

In most of our client's formulation development projects, we have generated new intellectual property for them that provides additional layers of protection and exclusivity. Our team members have been invited to chair and speak at national and international conferences and symposia in the areas of formulation development and hot-melt extrusion. Many of our clients come to us through word-of-mouth referrals, management personnel who have moved to another company, or companies directed to us by venture capital investors who saw what we were able to do for another of their portfolio companies.

Q: What is your unique approach to solving product development challenges?

A: Our approach to solving product development challenges is to begin with the basic research needed to understand the source of the challenge or problem, whether it be a solubility study, excipient compatibility study, or forced degradation studies. We integrate our drug delivery technology team with formulation development, analytical, materials, and manufacturing groups to communicate across the departments and work closely with our clients. Two, three, or more heads are always better than one.

We also assess the potential of novel delivery systems and evolving technologies to address client-specific needs. For example, we have developed pulsatile drug delivery systems, sustained-release liquid filled capsules, and products for delivery to the buccal mucosa and vaginal cavity in response to particular client needs. We are one of the few service providers with expertise in both nasal and pulmonary delivery. Our team and facility can provide clinical supplies for prototyping and proof-of-principle trials through commercial scale.

Q: How do you maintain robust quality systems for your customers?

A: Our Quality Assurance team stays on top of all quality systems and is involved in all aspects of drug product development, analytical testing, clinical trial manufacturing, and commercial manufacturing. Our state-of-the-art facility is approximately 50,000 square feet and registered with the US FDA and DEA. The FDA inspection was part of a pre-approval inspection that was successfully concluded without a 483. We have had about 100 client and consultant quality audits. Because we are DEA registered and licensed, we are regularly audited by the DEA as well. All employees are trained for compliance with GMP.

The facility is temperature controlled and continuously monitored. Our manufacturing personnel are highly trained and operate in multipurpose suites designed to support preparation of pharmaceutical dosage forms for clinical and commercial products. The production areas are continuously blanketed with single

pass, HEPA-filtered air. The production area has been designed to facilitate the simultaneous execution of multiple operations to expedite the manufacturing processes.

Q: How do you manage projects with your clients?

A: All of our projects have an assigned lead project coordinator who schedules regular teleconferences and meetings throughout the project. PharmaForm maintains an open-phone-line-approach to project management. Clients may contact any PharmaForm team member at any time. We provide meeting minutes and update reports as needed throughout the program. Programs are also actively managed using Microsoft Project. Gantt charts are routinely updated and provided to the client during the project.

Q: What proprietary technologies does PharmaForm offer?

A: Through our parent company, Akela Pharma, we have access to drug delivery platforms for pulmonary administration, transmucosal delivery, and oral sustained release. We have a proprietary multi-dose dry-powder inhaler, named Taifun™. The device combines integrated and patented deaggregation and humidity control systems that provide for highly efficient and reproducible powder flow. The patented LURUX® wet suspension technique ensures excellent powder homogeneity and dose-to-dose content uniformity. The mechanical robustness and flexibility of Taifun, its functional strength, and adaptability, coupled with a low manufacturing cost, position it as a very attractive dry powder inhalation platform. Salbutamol Taifun™, the first Taifun product, has been approved in 10 European countries.

Our oral sustained-release technology suite, PADT™, was developed to deter the abuse of scheduled products, including narcotics and stimulants, and prevent alcohol-induced dose dumping with any oral pharmaceutical product. Drug abusers typically prefer opioid and stimulant formulations that provide rapid absorption of the drug in order to obtain a desired euphoric effect. Abusers can bypass the sustained-release features of current products by crushing and mixing them with alcoholic drinks or by crushing and snorting or dissolving and injecting the drug. Our PADT systems provide a solution to this problem by virtue of a dosage form that is very difficult to crush or chew. Our PADT systems also prevent alcohol-induced dose dumping and alcohol extraction by maintaining sustained-release characteristics in 40% alcohol, comparable to the release in water or normal dissolution media, for more than 3 hours.

PharmaFilm™, our transmucosal delivery system, is a patented, bioadhesive, thin film for delivery to the buccal mucosa and gingival, rectal, vaginal, and dermal surfaces. Current prototypes have demonstrated in vitro release times ranging from 5 minutes up to 24 hours and in vivo release times from 15 minutes to 20 hours, depending on the half-life of the active therapeutic agent. The film can be produced in single or multiple layers and is suitable for combination therapies.

Q: What are you seeing in terms of the use of outside resources?

A: We are finding more and more that client companies are looking for external resources to help them find a better solution, faster. It often isn't just a question of sourcing additional expertise, it is also a question of getting more hands to move the project to the next milestone more quickly. By providing our clients with proposals that outline the project costs and timelines, they are better able to budget their resources and manage internal expectations. We expect to see a continuing movement to outsourcing critical path activities to experienced companies like PharmaForm as well as technical challenges for which there are limited internal resources. ◆

Is Your Organization Effectively Positioned for Growth in the Drug Delivery Market?

As a result of developments in the pharma industry, the drug delivery market is poised to undergo rapid expansion. Pharma, Specialty Pharma, and Biotech companies will continue to seek partnerships with Drug Delivery companies that expand their product development options. Is your company positioned to take advantage of these opportunities for growth?

Frost & Sullivan's Pharmaceutical & Biotechnology group provides market intelligence and consulting support to identify and take advantage of the best growth opportunities in the Drug Delivery market.

Our expert Healthcare analysts:

- Provide objective, 3rd party analysis
- Identify a range of growth options
- Evaluate which options will produce the best Return on Investment
- Work with clients to develop effective implementation strategies

For more information on growth opportunities in the Drug Delivery market, please contact Melina Trevino at melina.trevino@frost.com.

FROST & SULLIVAN

Technology Showcase

Innovative Platforms

Adhesives Research has over 20 years of experience manufacturing pressure-sensitive adhesive systems for the pharmaceutical industry. Adhesives Research's custom development capabilities include polymer synthesis, adhesive mixing, compounding, coating, and release liner design, supported by analytical capabilities. The company integrates these capabilities to formulate and manufacture unique products to meet customers' specifications. The company's Pharmaceutical division provides skin-friendly adhesives and laminate for active and passive transdermal delivery systems and pulmonary delivery applications. ARx, LLC (a wholly owned subsidiary of Adhesives Research) addresses the growing global need for innovative delivery of active drug-containing systems. ARx develops and manufactures innovative pharmaceutical products, including adhesive laminates and dissolvable films, for customized drug delivery platform technologies. For more information, contact Adhesives Research at (800) 445-6240 or visit **www.adhesivesresearch.com**.

Capsule Filling & Sealing

Designed to allow formulation scientists the ability to better exploit the potential of lipid-based formulations for poorly soluble compounds, the CFS 1200 helps accelerate the development timeframe and achieve Faster Time to First in Man. A fully automatic cGMP-compliant machine, it fills and seals up to 1,200 capsules per hour with liquid or semi-solid formulations without banding. It is designed for ease-of-use and high reliability, with the ability to quickly clean and change capsule sizes with available change parts. Product integrity is ensured with gentle handling of capsules before sealing and during the drying cycle. Other features include a robust filling pump with highly accurate temperature control, improved capsule manipulation before sealing and during drying using new "Cap-edge" handling system, and improved design of filling and sealing process that ensures better control and cleanability. Fore more information, contact Capsugel at (888) 783-6361 or visit **www.capsugel.com**.

Topical Formulations

Dow Pharmaceutical Sciences, Inc.
The D in Topicals R&D
Since 1977

When you work with Dow, you can feel comfortable in knowing that your product is in very experienced hands because we focus only on topical formulations. After 31 years, we know how to prevent the unique problems that often occur during topical formulation development, analytical method development, scale-up, and long-term storage. In just the past 3 years alone, we helped 65 clients develop stable, elegant, scalable formulations that are disease compatible and penetrate the skin or ocular tissue as required. This is accomplished by a team of formulation, analytical, and drug transport scientists using Dow's unique formulation development process. For more information, contact Dow Pharmaceutical Sciences, Inc. at (707) 793-2600 or visit **www.dowpharmsci.com**.

Polymers & Delivery Technologies

Pharma Polymers is one of the world leaders in the manufacturing and supplying of functional coatings for the pharmaceutical industry. EUDRAGIT® polymers are ideal for enteric delivery, controlled release, and protective coatings. Based on more than 50 years of experience in EUDRAGIT polymer design and formulation know-how for pharmaceutical applications, Pharma Polymers has developed intellectual property on advanced oral drug delivery technologies. The different brands of EUDRAPULSE®, EUDRACOL®, and EUDRAMODE® are the achievements of this intensive research and development effort so far. Pharma Polymers' business models for commercialization of these drug delivery technologies range from the development of customer-specific solutions to out-licensing strategies. For more information, contact Evonik Degussa Corporation at (877) 764-6872 (option 4) or visit **www.pharma-polymers.com**.

Technology Showcase

Learning Tool

PARTNERING SUCCESS: The Challenge© is an innovative learning tool created by The Learning Key, Inc. The business-based board game provides trainers and participants an interactive approach to learning the ins and outs of strategic partnering and outsourcing. It provides a valuable forum to discuss your company's outsourcing strategies and approaches in creating long-lasting partnerships. The game is designed to improve employee understanding of the stages of outsourcing and partnering; give employees new insights into ways to enhance partner relationships quickly and efficiently; encourage teams to work together solving problems, taking risks, and making decisions; and make learning fun and memorable. For more information, contact The Learning Key at (800) 465-7005 or visit **www.thelearningkey.com**.

Niche Generics & DPI

PH&T is an Italian pharmaceutical company engaged in research, development, and production of generic drugs for specialist therapies and innovative medical devices, to be sold through licensees and distributors. PH&T selects products, mainly in niche areas, that are both scientifically sound and technically complex. The Company has a wide range of experience in the development of oral slow-release formulations, nasal sprays, and injectable products and in product registration in Europe throughout multistate and decentralized procedures. Quality of the product, careful selection of client companies, reliable assistance in regulatory affairs, and active marketing support in the commercial phase are PH&T keys to success. PH&T has also developed and patented Turbospin®, a simple and effective single-dose, multi-use DPI. For more information, visit PH&T at **www.phtpharma.com**.

Global Central Labs

PPD

PPD'S GLOBAL CENTRAL LABS
A 20 Year History of Success
A FUTURE OF ENDLESS INNOVATION

No one gets medicine into the system faster®

PPD's global central labs fully support your drug development programs with extensive global reach; logistical expertise; highly customized and flexible services; strong and consistent science and therapeutic expertise; high-quality performance (98.5% data acceptance rate); efficient, accurate, and rapid sample collection; and state-of-the art laboratories with all relevant accreditations and certifications. Through strategically located facilities in North America and Europe, and with the use of sophisticated logistics and courier services, PPD provides clinical laboratory services to investigator sites in virtually every country of the world. PPD recently announced it has expanded its global central lab services into China through an exclusive agreement with Peking Union Lawke Biomedical Development Limited. For more information, contact Rob Danziger at (859) 442-1300 or visit **www.ppdi.com**.

Drug Development

Xcelience®
www.xcelience.com
Tampa, FL

Xcelience is the premier source for unsurpassed quality in drug development services. The company brings together the industry's most experienced and talented scientists, consistently and efficiently moving compounds through the research and development continuum to regulatory approval. Since 1997, the Tampa-based laboratory has been developing formulations for clients throughout the pharmaceutical industry. Xcelience's unique corporate structure creates project teams that work intensively with each client, bringing an extension of their own organization into the Xcelience lab. The lab uses only state-of-the-art equipment, highlighted by the patented Xcelodose®, which fills API directly to capsules (Xcelodose is a registered trademark of Capsugel BVBA). This and other technologies give Xcelience unparalleled speed to market without compromising its absolute commitment to quality. For more information, contact Xcelience at (608) 643-4444 or visit **www.xcelience.com**.

DRUG DELIVERY Executive

dermaCM: A Contract Manufacturer With Advanced Nanotechnology

Robert L. Dowdell
Executive Director of Sales
dermaCM

"We believe the NLP and SDMC applications in pharmaceuticals and nutraceuticals is limited only by our imagination, enabling our customers to differentiate their brands with superior and proprietary product performance capabilities."

dermaCM is a state-of-the art FDA-registered facility located in St. Petersburg, Florida. The company develops and manufactures OTC pharmaceuticals, nutraceuticals, and dermatological products. Further, the company provides a range of analytical, microbiology, and research services. The parent company has been at the cutting edge of nanotechnology research for 18 years and has incorporated its Solvent Dilution MicroCarrier (SDMC) all-natural nanotechnology in a wide range of topical products, including sun care products marketed globally. As a progression from the SDMC technology, dermaCM has recently announced the offering of its patent-pending nano-lipidic particle technology (NLP), which has many uses and some advantages over the SDMC technology. A recent NLP study has illustrated considerable success with the application of taste-masking in beverages. Test marketing has been carried out on a sport's beverage using the taste-masking ability of the all-natural nanotechnology to mask the taste of electrolytes in the beverage. These technologies are now available via licensing agreements through dermaCM. Drug Delivery Technology recently interviewed Robert L. Dowdell, Executive Director of Sales for dermaCM, to share his thoughts on how dermaCM is making significant inroads in the development of drug delivery technologies, while providing a full suite of contract manufacturing, research and development, and technologies licensing services.

Q: Can you please tell our readers about the history of dermaCM?

A: dermaCM is a division of parent company Dermazone Solutions, Inc. We were formed in 2006 when Dermazone recognized there was a need in the contract industry for pharmaceutical standard manufacturing combined with nanotechnologies to provide clients with proprietary formulas. Our mix of quality standards and technologies coupled with comprehensive research and development capabilities guarantee superior formula performance as well as a measurable and definable product-marketing edge for clients. The proprietary SDMC development began with research into formulas to treat deep scarring from burns and continued over the course of 18 years. Burn victims need a penetrating delivery system that can provide a consistent, sustained release of healing ingredients. During these early days, the company focused its research on potentiating the effectiveness of silver sulfadiazine and improving delivery of encapsulated healing ingredients into the skin. The outcome was Dermazone's patented Lyphazome® nanotechnology delivery system which, throughout the years, has proven to be a very effective means of not only delivering much needed healing ingredients for the treatment of deep burns, but also for achieving superior topical delivery and sustained release in cosmetic, cosmeceutical, and pharmaceutical applications.

Q: How are your unique technologies used for drug delivery?

A: Lyphazome nanospheres, a fraction of the size of traditional liposomes, are generally recognized as safe by the FDA for topical and oral use. Lyphazome technology is completely natural and metabolized by the body, thereby eliminating the risk often associated with synthetic material(s) often used for sustained-release delivery. From this initial development, the company discovered the next generation of microspheres; nano-lipidic particles (NLPs) that measure between 30 and 200 nanometers. These NLPs form the building blocks for the nano-scale assembly of the second-generation particle system. The flexibility of these technologies allows for either an in situ or pre-load encapsulation depending on the client's needs and objectives. We've coupled this advanced technology with the ability to deliver 5-year stability and provide ease of manufacturing and formulation, bringing dermaCM to the forefront of controlled-release manufacturing.

Q: What services can dermaCM provide drug manufacturers?

A: dermaCM licenses both its SDMC and NLP delivery systems and offers formulating, private labeling, manufacturing, packaging, and fulfillment services supported by stringent adherence to FDA regulations for OTC pharmaceuticals. We can facilitate production for a wide range of companies (domestic and international), including large pharmaceutical firms seeking overflow facilities that will measure up to their stringent standards. Key differentiators of dermaCM include our ability to provide proprietary NLP and SDMC delivery systems, our highly skilled and qualified personnel, and our flexibility of batch sizes.

Q: Will you license formulas to manufacturers who do not want to outsource to your facility?

A: Apart from providing a state-of-the-art manufacturing facility, dermaCM will license our technologies directly to companies for product manufacturing. Further, we can provide contract expertise to companies wishing to utilize our technologies in their own facilities. Lastly, our contract laboratory offers a variety of market-tested formulas for immediate private labeling, with and without our nanotechnology platforms.

Q: How is dermaCM continuing to advance the drug delivery industry?

A: dermaCM has just announced the results of a double-blind test confirming the effectiveness of using NLPs to mask tastes in beverages. Benefits of taste-masking in drug delivery included improving consumer acceptance, patient compliance, and user satisfaction. These NLPs are safe and all-natural and feature high-loading capacity of passenger molecules, clear appearance, control of population size, a 30-nm to 200-nm range, and are inherently non-precipitating. We believe the NLP and SDMC applications in pharmaceuticals and nutraceuticals is limited only by our imagination.

Q: Will these taste-masking formulas be appropriate for lozenge or "quick-dissolve" orally disintegrating tablets (ODTs)?

A: dermaCM NLP technologies provide an efficient and optimized technology platform that may function as a stand-alone taste-masking product or as an integral component in troches or in ODT-enabled products. The size of the NLPs provides a particle size sufficiently small enough to overcome the capacity for particle detection in the oral cavity while providing a pleasant mouth feel. The composition of the NLP provides a completely natural material for formulation with an extremely wide range of capacity for passenger molecules. The use of soy phospholipids in dermaCM NLP products overcomes many of the short comings of traditionally prepared coated particles, including hydroxypropyl methylcellulose, polyvinylpyrrolidine, ethycellulose, methacrylates, and other substances by providing a totally metabolized product. NLPs are compatible with a wide variety of commercially

available oral products, including liquid formulations, tablets, dried films, and wafers.

Q: Who are some of your OTC customer and/or successes?

A: Our commitment to client confidentiality precludes our disclosing specific names; however, we can reveal that dermaCM manufactures for and licenses its technologies and numerous OTC formulas to several domestic and international companies. These customers are able to penetrate and dominate both market share and channel(s) of distribution by differentiating their OTC brands with superior and proprietary product performance capabilities using our SDMC and NLP nanotechnologies. Our technologies have been used with great success in at least four major sunscreen brands marketed globally. In these topical applications, "size matters." The primary key to the effectiveness of any topical formula that uses nanotechnology lies not only in the size of the product's nanosphere delivery vessels but also in the consistency of the size of the nanosphere produced within the formulation. Size consistency is critical for uniform topical distribution of active ingredients. These nanospheres are small enough to easily penetrate the skin's natural surface barrier, yet large enough to not be counter-productively absorbed by the body. dermaCM-produced products can be designed to time-release deep into the epidermis an 80% concentration of nanospheres containing effective ingredients. In doing so, we create a product superior to those in which ingredients are released at the skin's surface levels. These nanospheres build up a reservoir within the stratum granulosum where they remain poised, much like "smart bombs," ready to penetrate deeper into the skin as needed over time. As they migrate through the deeper epidermis layers and further disperse, the nanospheres time-release their encapsulated ingredients. The remaining 20% non-encapsulated ingredients provide immediate surface benefits. Clients whose products are formulated to these standards are able to increase market share by differentiating their formulas as durable; high-performance; and all-day waterproof, rub-proof, and sweat-proof.

Q: What additional technologies is dermaCM developing?

A: dermaCM is currently engaged in the development of a third-generation SDMC technology that will lead to finely controlled-size populations via lyophilization and sponge applications. Our future efforts will also include the development of applications for intravenous and inhalation drugs, as well as examining the effectiveness of improved solubility for active pharmaceutical ingredients, veterinary ingredients, and nutraceuticals.

Q: What are the advantages for drug manufactures in using contract manufacturing, research, and packaging?

A: There are many advantages in using a contract manufacturer. One of the most common reasons is flexibility of supply, which means that without the need to maintain high inventory levels of raw materials etc., the end result is normally cost effective. If a good relationship is developed with the contract manufacturer, that relationship effectively makes the manufacturer an extension of the company, which of course, benefits both parties. In the areas of research and development, there are potential cost savings if some projects can be handled by a competent contract manufacturing facility. Also, licensing partnerships for unique ingredients, formulas, and technologies are often discovered through a contracting partnership. When choosing a contract manufacturing company, one of the major considerations should always relate to the quality and abilities of the research and development and other technical personnel at the company. This is as important as finding a manufacturer with the ability to simply produce the desired product type. ◆

Does your patent firm dig deep for the right answer?

Davidson, Davidson & Kappel, LLC
Extensive pharmaceutical patent expertise:
Patent procurement | Due diligence/Opinions | Litigation

Dedication
Diligence
Knowledge

For more information, contact:
Cliff Davidson, Esq.
Davidson, Davidson & Kappel, LLC
485 Seventh Avenue New York, N.Y. 10018
Telephone: (212) 736-1940
E-mail: cdavidson@ddkpatent.com
Visit our website: www.ddkpatent.com

SPECIALTY PHARMA
Strategies For Business Development

Mark A. Goldberg, MD

President of Clinical Research Services & Perceptive Informatics
PAREXEL International

Lily Li

Laboratory Director
Tandem Labs-New England

Timothy Scott

President
Pharmatek Laboratories

Bill Sharbaugh

Chief Operation Officer
PPD

CRO Strategies

Specialty Pharma Makes CROs Part of Its Pipeline Strategy

By: **Cindy H. Dubin,** Contributor

As the 17th Annual *Partnerships with CROs* conference kicks off this month in Las Vegas, the industry is buzzing with today's hot topics in outsourcing — performance metrics, diversity, and challenges in clinical trials. Throughout the past decade, increasing pressure to reduce costs and time-to-market has lead to a rapid expansion of the global CRO market, according to Research and Markets' report *The CRO Market Outlook*. Pharmaceutical and biotechnology spending on CRO services has shown double-digit growth in the past years, highlighting the importance of this fast growing market.

The report shows that the total CRO market size was estimated at $14 billion in 2006 and is expected to grow at an annual rate of 14% to 16% to reach $24 billion through 2010. A profile of the CRO market shows that it is highly fragmented, and the number of CROs worldwide has reached more than 1,100 despite continued consolidation. Clinical trials conducted by CROs are completed up to 30% more quickly than those conducted in-house by pharma companies. This results in an average time savings of 4 to 5 months, translating to $120 million to $150 million in increased revenue potential. The leading CROs are commodity full-service providers, acting as one-stop shops for all services, from preclinical through marketing.

In this second annual report, *Specialty Pharma* magazine asked some of the leading CROs how they are addressing the important issues of today and what they are doing to distinguish themselves from the rest of the crowd. Participants in this discussion include Mark A. Goldberg, MD, President of Clinical Research Services and Perceptive Informatics, PAREXEL International; Lily Li, Laboratory Director, Tandem Labs-New England; Timothy Scott, President, Pharmatek Laboratories; and Bill Sharbaugh, Chief Operation Officer, PPD.

Q: *How are the performance metrics of time, cost, and quality affecting your relationships with Specialty Pharma clients?*

Dr. Goldberg: A recent survey produced by Health Industry Insights, an IDC company, and sponsored by PAREXEL, reported that the top three most important performance metrics for biopharmaceutical companies, including Specialty Pharma, in working with CROs on clinical studies are: meeting milestones, keeping the project on time, and keeping the project on budget. A Tufts Center for the Study of Drug Development survey conducted for the Association of Clinical Research Organizations (ACRO) concluded that high CRO usage projects are submitted more than 30 days closer to their projected submission date than are low CRO usage projects. The study found that in addition to completing projects faster with extensive use of CROs, sponsors maintained a comparable level of quality. As recent industry research indicates, leading global service providers, such as PAREXEL, are helping clients improve performance of their clinical development programs. PAREXEL is working with Specialty Pharma companies to leverage technologies that can decrease the time and cost of clinical development while bringing increased quality and efficiencies to clinical trial management. Our data-driven patient recruitment, for example, utilizes tools for more accurate last-patient-in (LPI) predictions, which are critical components to any successful program. When incorporated early enough, predictive tools can relieve the patient recruitment bottleneck, helping sponsors reduce costs involved in bringing new products to market faster. We are also helping clients use Electronic Data Capture (EDC) to enable more effective information flow across various functions and organizations involved in executing clinical studies and developing products. Companies that are facile in deploying and using EDC globally will increasingly have an edge, and those who view EDC as one component of a total eClinical solution can expect to realize significant improvements in efficiency and data quality in clinical trials.

Mr. Scott: When Pharmatek was founded in 1999, our founding principle was to deliver quality services to the pharmaceutical industry. This was a non-negotiable principle upon which we built the company. Quality is what our corporate culture is built on — quality people, quality systems, and quality communications. It is what attracts employees to the company, it is what excited clients about Pharmatek, and it is what drives our earnings. Timing is often the most pressing issue for Specialty Pharma, as they typically operate under tight development timelines. Competing on the basis of time means maintaining sufficient staff to optimize development time and run our manufacturing operations to maximize turnaround. To help address these pressures, Pharmatek has developed a system for improving manufacturing scheduling time based on queuing theory. Application of this mathematical model to our manufacturing schedule has allowed us to shorten the wait time for moving client projects into our manufacturing suites.

Cost is a combination of the quality of work performed and the people performing that work. As it turns out, the combination of our efficient systems and our high-quality standards results in pricing that is competitive in the marketplace.

Ms. Li: We work with an extremely wide variety of clients — from virtual and consultants to the largest pharma organizations. We have observed that many of these organizations are waiting to ensure the endpoints were met positively for a previous study before approving activity on their next study. This puts more pressure on the CRO with respect to resource planning. It's critical for CROs to properly budget for instrumentation and more importantly, hire and train scientists. Therefore, the ability to plan as far in advance as possible is extremely important. There does not appear to be a good correlation between price sensitivity and the size of our client's organizations. The primary focus is on time and quality. Price is important, but secondary to time and quality. However, this may be a result of the types of clients Tandem works with. We focus on partnering relationships vs. vendor relationships. Tandem is committed to partnering with clients for the long-term, not just individual projects. Tandem has always focused on communication, compliance, data quality, and scientific integrity. The competitive nature of the CRO industry combined with pharma organizations looking for ways to cut research costs will always drive prices lower. Therefore, it is even more critical for us to assess market changes, technology improvements, and fund internal research into technology, processes, and the science behind our work and balance these with our clients' needs. This approach appeals to our clients. This is why Tandem Labs established a pure Research and Development group, which has already resulted in US patents.

Mr. Sharbaugh: Drug development costs are steadily rising, and both pharmaceutical and biotech companies are under pressure to contain costs. Outsourcing is a viable strategy to shift large fixed costs to variable costs. Whether a large or small drug developer, buying the services you need, when you need them, from a CRO with a proven track record makes financial sense. Companies can further leverage cost structure by reducing the need for internal oversight of a CRO partner, which requires selecting a full-service CRO with global reach, a good master service agreement, communication, and trust. As strategic outsourcing partners, CROs should use a variety of metrics,

including cycle time, quality, and cost to measure performance and business outcomes. Metrics are valuable because they keep discussions of performance grounded in data and facts. At PPD, we stack up well when comparing our performance to individual companies or industry benchmarks. Based on our global capabilities and size, we are able to achieve economies of scale and efficiencies, which can be challenging for any single biotech or pharmaceutical company.

Q: *How have you had to adjust to comply with clients' financial models?*

Mr. Scott: Gone are the days of slow and expensive drug development cycles and large pharma's deep pockets for drug development. For many Specialty Pharma companies, success may hinge on a single compound and all of the company's resources are focused on pushing that compound through the development process as efficiently as possible. Pharmatek is focused on helping companies do just that. Our goal is to help our clients take their compounds from discovery to the clinic as quickly as possible with a formulation that is scalable, easily transferable, and scientifically sound.

Mr. Sharbaugh: We understand that the needs of each client may vary, and PPD uses a variety of financial models to meet those needs. We typically structure master service agreements for larger clients who have a significant amount of repeat business. For smaller clients, we are able to structure task orders for individual projects. The majority of our clients use a full-service outsourcing model, but we also support other models, such as functional outsourcing, dedicated staff, and a risk-sharing model we call compound partnering. In addition, some of our biotech or smaller pharma clients are often in the process of raising capital, and we work with them under those circumstances.

Ms. Li: We have several product lines, and each can work with different groups within a given client. Therefore, we have to work with each client to understand what is important to them. Understanding the clients' scientific needs typically provides a logical study design to answer the key questions while taking the financial aspects into consideration. Because clients are more effective in halting development for compounds that may present development issues, there are more preclinical studies and less large clinical studies. While many competitors have publicly stated they will focus on larger clinical studies, Tandem Labs has adapted and learned how to become efficient working with many clients and numerous small studies, each of which often lead to the larger clinical programs.

Q: *What have you done to bring diversity into your work for clients?*

Ms. Li: In addition to the dedicated Research and Development group, Tandem added a dedicated non-GLP mass spectrometry services group including rapid turnaround time pharmacokinetic and pharmacodynamic studies, structural elucidation, and targeted biomarker studies in Woburn, MA. We have also expanded our GLP immuno-analytical capacity, which includes pharmacokinetic, immunogenicity, and cell-based assays. We are also planning on establishing both non-GLP mass spectrometry services and GLP immuno-analytical services in the San Diego area in 2008.

Mr. Sharbaugh: Global diversity is one way we are expanding to meet our clients' needs. As a service organization operating in 40 countries, our most important asset is our people. We seek to identify, recruit, and retain a global, diverse work force to help us meet the goals of our clients. Nearly one-third of our work force is based outside the US, and 34% of our revenue was generated outside North America in 2007. We expect both of those numbers to continue to grow as more of our clients are looking to move into new geographic markets and expand their clinical trials programs globally. In the past few months, we opened offices in Portugal, Peru, Australia, and Denmark and expanded our footprint in existing locations, such as the UK and India. In February, PPD announced plans to purchase InnoPharm, a CRO based in Russia and Ukraine. We will continue to make niche acquisitions that increase our scope or expand our services. PPD has a global workforce and local expertise on the ground to assist clients in meeting their overall program goals while maintaining regulatory compliance and patient safety.

Q: *What are you doing to break from the CRO pack and become a choice provider?*

Dr. Goldberg: PAREXEL helps companies successfully develop and commercialize products for regional and international markets by utilizing our extensive expertise, advanced technologies, and global presence. We had the foresight to predict the globalization of clinical research, leading us to expand our global footprint and provide access to a wide array of geographies for clients' programs. PAREXEL has anticipated client demand for resources and capabilities in established locations as well as emerging geographies for clinical research, and now operates in 64 locations throughout 51 countries. PAREXEL has recently expanded further into high-priority, emerging locations for clinical research. For instance, with our acquisition of APEX International in 2007, PAREXEL is able to provide clients with a wide range of clinical research service offerings throughout 11 countries in the Asia-Pacific region. PAREXEL continues to invest in our technology platform to meet evolving client needs. We are a front-runner in leveraging eClinical technology in the execution of clinical trials. Additionally, through our subsidiary, Perceptive Informatics, we provide technologies to facilitate the clinical development process, including medical imaging, Interactive Voice Response Systems (IVRS), and Clinical Trial Management Systems (CTMS). Perceptive is a leader in several technology areas. For instance, Perceptive has significant experience in novel medical imaging modalities, and medical imaging is increasingly serving as an endpoint in determining the safety and efficacy of new treatments in clinical trials. The Perceptive Informatics IMPACT software is a market-leading clinical trial management system with more than 26,000 users in over 85 countries — the largest number of users of any CTMS solution on the market. PAREXEL has in-depth expertise in integrated clinical development, medical communications, and regulatory affairs. We have more than 7,300 employees, and many leading experts who are recognized thought leaders on various topics, including regulatory affairs, clinical development strategies, eClinical technology applications, and biopharmaceutical portfolio management. PAREXEL has experience with thousands of studies across the globe, and our medical directors and scientists have extensive expertise in all major therapeutic areas.

Global Clinical Supplies + Services. Integrated.

Bilcare's Promise to You

When you partner with Bilcare, you'll receive:

- Expert guidance based on deep industry experience;
- Excellent quality, beyond compliance;
- Energetic personal service that's engaged and detail oriented.

We guarantee specialized support and services tailored to your individual clinical trial needs on a global basis. We deliver personal service that's prompt, flexible, timely and in a quality manner.

- **+ Clinical Supplies Project Management**
- **+ Formulation Development**
- **+ Analytical Research Services**
- **+ Clinical Manufacturing, Packaging and Labeling**
- **+ Interactive Voice/Web Response System (IVRS/IWRS)**
- **+ Global Logistics and Distribution**
- **+ QP Services**

Visit us at Partnerships with CROs, Booth #622

Bilcare
Global Clinical Supplies

Americas + Europe + Asia
Service and Quality Beyond Compliance

Call 800-310-4445, Email direct-gcs@bilcare.com or visit BilcareGCS.com today.

Mr. Sharbaugh: Our unique compound-partnering program is certainly one area that sets us apart from other CROs. We use our discovery and development capabilities to form partnerships with sponsors, sharing in the risks and rewards of developing new molecular entities. PPD shoulders the expense of development usually from lead compound (pre-IND) through Phase II proof-of-concept. The compound is then licensed to a commercial partner for development through NDA and commercial launch. PPD gets milestones and royalties on sales. A recent example is a DPP-4 inhibitor for the treatment of type 2 diabetes. PPD has partnered with Takeda throughout the past several years to bring this important product to market, and the compound was recently accepted for filing by the FDA.

Ms. Li: Beyond typical LC/MS/MS-based bioanalysis, our broad expertise and bioanalytical research has allowed us to become experts in dealing with ionization matrix effects prevalent in mass spectrometric analysis and the analysis of both chiral analytes, peptides, and oligonucleotides, and a broad range of tissues for both GLP and non-GLP studies. We are also leaders in IT-based solutions to GLP requirements and laboratory operation. Tandem has many clients that focus on ocular tissue analysis, which has led us to become experts in this area. As mentioned earlier, we also accommodate small studies, small companies, and in all cases, work to become an extension of our clients operations. We have also added several services, including non-clinical formulation analysis, pharmacokinetic, and toxicokinetic reporting. We want to partner with our clients; therefore, we work hard to establish an understanding of our clients' experiences in bioanalysis and adjust our communication and relationship to their needs.

Mr. Scott: Pharmatek focuses on early phase, preclinical to Phase II, development projects. This focus enables us to be more responsive and flexible to our client's timeline requirements and cost structures, while providing a high-quality product. The decisions, science, and factors that affect early phase development differ significantly from those affecting Phase III and commercial development. By focusing on early phase development services, we are able to concentrate our expertise and resources on getting the client from discovery into the clinic as efficiently as possible. Employee turnover is a tremendous expense for CROs, and most CROs average 20% to 30% annual turnover. Pharmatek distinguishes itself from other CROs by investing in programs that create high employee retention. A combination of corporate culture that respects our scientists as a valuable member of the company, our employee development programs, and our succession planning programs help ensure a turnover rate far below the industry norm. The benefits to our clients are twofold: 1) they experience greater consistency in project management; and 2) they receive savings passed on from our reduced cost for recruitment and retraining.

Q: *What are you doing to ease client challenges of conducting clinical trials in today's regulatory environment?*

Ms. Li: While Tandem Labs has diligently worked at building a reputation for excellence in bioanalytical mass spectrometry and immuno-analysis as well as providing a challenging environment for skilled scientists to grow, we have also worked at maintaining a strong business and financial focus. This includes formal and informal relationships with clinical providers (such as Qualia), preclinical service providers, and pharmacokinetic and toxicokinetic consultants. This strategy has resulted in the recent acquisition of Tandem Labs by Esoterix Clinical Trials Services. With this new organization, Tandem Labs can continue to provide the highest quality bioanalytical services while expanding its association with clinical service providers. Each of these providers is an expert in their field as well as with regulatory challenges. Tandem Labs specifically is focusing on meeting current regulatory challenges by allowing open access audits to its operations by our numerous clients. These audits combined with our participation in industry meetings and focus on technology and/or IT-related solutions to regulatory challenges allows us to stay in the forefront of regulatory trends and anticipate changes well in advance.

Mr. Sharbaugh: The recent passage of the FDA Revitalization Act reflects the current regulatory environment in which sponsors, regulators, and other stakeholders are re-thinking the risk management paradigm. At PPD, we are realigning our business to help clients develop risk management strategies in both the pre- and post-approval environment. Outcomes research, pharmacoeconomics, registries, and observational studies, as well as overall post-approval commitments, are areas in which we assist our clients.

Mr. Scott: Pharmatek eases clients' regulatory challenges by designing formulations that are as simple as possible relative to the scientific requirements of that formulation, providing reports that are FDA and EU ready, and performing science that is data-driven. There must be a sound scientific basis for the formulation that we provide. And we must be able to provide the regulatory documentation to support that science.

Dr. Goldberg: PAREXEL Consulting experts, many of whom are former regulators, build and maintain strong and transparent relationships with regulatory authorities throughout the world. These experts have scientific, regulatory, and business expertise and understand the entirety of the issues that may impact regulatory thinking in areas such as drug safety, pricing, reimbursement, clinical trial design, and GxP compliance.

Our consultants work closely with Specialty Pharma companies, many which have niche therapeutic focus areas and need to actively acquire product assets, to help them conduct the required due diligence or determine the right drug delivery methods, for instance. Many Specialty Pharma companies turn to PAREXEL Consulting to in-source non-core competencies in order to gain needed expertise and reach new global markets. Specialty Pharma companies are facing increasing scrutiny with respect to drug safety issues, and PAREXEL is helping clients take a proactive approach to pharmacovigilance. We help clients incorporate safety considerations and risk management into their drug development programs — from the earliest stages through the entire development lifecycle, including all phases of clinical development and post-marketing surveillance. Our global team of safety physicians, scientists, pharmacoepidemiologists, and regulatory experts provide a wide array of support, including adverse event management, regulatory reporting, and design and maintenance of global safety databases. As a myriad of regulatory, medical, and scientific issues related to clinical development have created a rapidly changing environment, PAREXEL and our technology subsidiary, Perceptive Informatics, have been committed to easing these challenges for our clients. An example is our ability to assist clients in taking advantage of medical imaging and other biomarkers as surrogate endpoints in the evaluation of the safety and efficacy of new products. ◆

PPD's Global Central Labs

Transforming Sample Management

Success should never be taken for granted...

so at PPD's global central labs, we work hard to make sure you are in control of your study goals and in touch with your samples to ensure their life cycle is successful.

As the testing industry evolves and your needs change, PPD is taking a fresh look at sample management and redefining it. We're not waiting for the future, we're shaping it.

Technology you can count on

- Unique labeling system for accurate sample tracking
- Temperature-controlled specimen storage
- 24/7 data access, monitoring and flexible reporting

Results you can bank on

- Fast start-up & on-time data delivery help you be first to market
- Vendor contracts save on transportation costs
- Tight quality controls minimize errors

The people who make it happen

- Expert consulting
- Dedicated project management
- Highly trained site personnel

Call Rob Danziger at +859 442 1300, e-mail us at **labs@rtp.ppdi.com** or visit us at **www.ppdi.com**

Millions of Samples Successfully Managed

PPD'S GLOBAL CENTRAL LABS
A 20 Year History of Success
A FUTURE OF ENDLESS INNOVATION

PPD®

PRECLINICAL/PHASE I > PHASE II-IIIb > POST-APPROVAL > **LABS**

No one gets medicine into the system faster®

Marketing Strategies

Quality, Solution, Leading & Experience: It's all too Predictable

By: Malcolm A. Teasdale, Big Idea Catalyst, Teasdale Worldwide

Once you've decided that your marketing is serious business, you'll need to move forward with a detailed game plan. Many of you are finding out that marketing is the key ingredient to gaining market share and keeping it. I still see so many companies that just "wing it." If it feels good or it's a good deal, then they'll do it. No strategy involved; they make up their minds as they go. If your marketing and advertising initiatives are not a line item on your budget, then do it at once! If you haven't properly researched your prospects and customers - and I don't mean a customer satisfaction survey that makes you feel good about the job you are doing - then you need to dig down and find out what makes your customers tick. What are they looking for? Their preferences and differences are key in creating the right messaging.

In just about all areas of life, we want to be like someone else. When we see people who are successful, we want what they have. We want to act like them, talk like them, make decisions like them, and even look like them. I believe it may be a comfort zone for most people; we are taught at a very young age to act and think like others. You remember hearing remarks like "Why can't you be like your brother?" or "You act just like your father!" or "Why don't you study law like your buddies?" Sometimes people want to be like others and not stand out from the crowd. How many times do you compare your company to your competitors? Do you lose out on new business to the competition and then wonder how you can emulate them?

It's not always that people don't want to stand out; it's just easier to copy what everyone else is doing. In fact, being different may be a bit uncomfortable because when you're different, you stand out. This is the premise that marketing is based on: standing out. Think about it, you invest in marketing so that people will notice your organization, and then you give them nothing to notice! You cannot expect results just because you purchased media space or advanced some publicity initiative; you have to stick out! The only way to stick out is to not copy everyone else in your industry. I have always said and believed that if everyone else is doing it, then don't!

If everyone claims to be the Leader, have the best Quality, provide the best Solution, and have the most Experience, then someone is lying. If so many firms are saying these things, who can your prospects believe? There are millions of words in the English language, yet everyone insists on copying each other with such profound words as Quality, Solution, Leading, or Experience.

How can anyone tell the difference between one company and its capabilities and another when everyone is using the same rhetoric? You'll be amazed when you take a peek at these claims from industry "leaders." The following are actual phrases from statements that companies are making (no doubt you have seen these countless times):

Has extensive ***experience*** at both…
Talent and ***experience*** of our team…
Scientific training and ***experience*** includes…
Our people have the expertise, ***experience*** and…
Highly ***experienced*** scientists…
Combined with new investment and ***experienced***…
Considerable skills and ***experience***…
The ***solution*** of choice for over…
Comprised of ***experienced*** industry professionals…
Most comprehensive and easy ***solution*** in the industry…
We can provide ***experienced*** consultants…
Automated ***solutions*** that maximize…
Our services and breadth of ***experience***…
Solution of choice for over…
Our ***experience*** in large …

Solutions that maximize efficiency and…
Experienced team and unique approach…
Business ***solutions*** providers with…
Our ***solutions*** provide fully integrated…
Experienced with the US FDA…
Customized ***solutions*** to the…
Experienced scientists are capable of rapidly…
And other pharmaceutical company ***solutions***…
Product development through knowledge and ***experience***…
Developing creative ***solutions*** to your unique…
Experience comes together with flexibility…
Customized product development services and ***solutions***…
Our team applies its extensive ***experience*** in…
Creative ***solutions*** to unique challenges…
We have unique ***solutions*** for unique projects…

Everyone claims to have some type of creative solution, yet I am sure most people have no idea of what that solution even is. In another unrelated industry, everyone is claiming to be the leader. Just take a look at the following claims, it's unbelievable!

Is a ***leading*** provider of fully…
Our industry ***leading*** software…
Associate yourself with the ***leader*** in…
Is an established ***leader*** in management…
The nation's ***leading*** and most…
The global ***leader*** in…
The ***leading*** provider of cost-effective…
The ***leader*** in web-based…
The ***leading*** industry solution providers…

A potential customer couldn't possibly tell you apart from the clutter; your name won't stand out when you're driving the same message that everyone else is. Beyond these meaningless words that everyone is throwing around, how do you break through? How do you move beyond empty claims and provide substance and value? INNOVATE.

Here is a definition of innovation: "the creation of substantial new value for customers and the firm by changing one or more dimensions of the business system."[1]

So start the process! You can't just re-package the same product or service (as good as it may be) that everyone else has. Innovative companies have no competition and truly own their market space. They are the only option customers consider and are never compared against any other provider. So how do you get there? Take a look at the 12 Dimensions of Innovation, or 12 different ways for your company to innovate[1]:

Offerings	**Customers**
Processes	**Presence**
Platform	**Customer Experience**
Organization	**Networking**
Solutions	**Value Capture**
Supply Chain	**Brand**

I am on a lifelong quest to get people to see the extreme value that only innovation can bring to an organization. Innovation is the key factor in the success of many organizations that we all envy today. It's those companies that are willing to go there that will greatly benefit in leading their industries and reaping the rewards of such bold thinking. ◆

REFERENCE

1. Sawhney M, Wolcott RC, Arroniz I. Center for Research in Technology & Innovation at Northwestern University's Kellogg School of Management.

Malcolm A. Teasdale

CEO
Teasdale Worldwide

Mr. Malcolm A. Teasdale leads the creative force and is the marketing expert behind Teasdale Worldwide, the Agency of Innovation that's creating edgy, effectual messaging while continuously applying his Marketing of Distinction™ — a revolutionary process that goes beyond the flawed nature of advertising. For more than 20 years, Mr. Teasdale has elevated the core practice of research combined with vivid imagination, resulting in client revenues that have increased from $48 million to $100 million over a 2-year period. As a sought-after speaker, his energetic style invigorates and brings a creative and motivational excitement to conferences, seminars, and results-driven workshops. He shares his expertise based on his extreme aversion to the fact that billions of dollars are wasted annually on advertising messaging that is completely ineffective. Methods to break through and overcome these pitfalls became the foundation for creating BRANDFiltration™, ChannelNSIGHTS™, and Intragrate-M™. He is the author of insightful articles and white papers and is currently completing his first book, Your Opinion Really Doesn't Matter (Your Customer's Does)™.

Executive Summary

Robert Zerbe, MD
CEO & Co-founder
QuatRx

QuatRx: Focusing on Late-Stage Development Programs in Major Therapeutic Areas

By: Cindy H. Dubin, Contributor

QuatRx is a privately held pharmaceutical company founded in 2000 and focused on discovering, developing, and commercializing compounds in the endocrine, metabolic, and cardiovascular therapeutic areas. The company, based in Ann Arbor, MI, has built a portfolio of late-stage clinical compounds targeting substantial and growing markets. All of the company's development-stage compounds have established clinical proof-of-concept, with the most advanced program, Ophena™, achieving positive pivotal Phase III results in January 2008. QuatRx owns full commercial rights in all major markets for its three current development programs and has out-licensed one compound in 2007. The company has shown success in attracting top-tier venture backers, most recently with a $44-million Series E financing in May 2007. Robert Zerbe, MD, CEO, and Co-founder of QuatRx, recently discussed with *Specialty Pharma* magazine the company's progress and key strategic decisions that have contributed to the company's rapid growth and success.

Q: ***What factors led to your becoming a founder of QuatRx?***

A: I was fortunate enough to be joined by three other senior executives (Stuart Dombey, Chris Nicholas, and Randy Whitcomb — all from Parke-Davis/Warner Lambert at the time of the company's acquisition by Pfizer) to form QuatRx in late 2000. We all had the opportunity to join Pfizer, but decided we were ready for new challenges and adventures. The company's focus has been in metabolic, endocrine, and cardiovascular diseases, which fits nicely with our backgrounds, particularly with our involvement in the development of Lipitor. Since QuatRx's founding, we have assembled, through licensing and acquisitions, a portfolio of four clinical-stage compounds.

Q: ***What makes the company unique, and what need is it meeting in the marketplace?***

A: The most unique aspect of our company is how advanced our pipeline is. All four of our clinical compounds have established clinical proof-of-concept. There are very few Biotech or Specialty Pharma companies that can make such a claim, much less those that are still privately held. We have chosen to out-license one of our compounds, becocalcidiol, which was licensed to CollaGenex Pharmaceuticals in 2007. However, we retain all commercial rights to all of our other programs in the major markets. We believe this is a sound strategy for any pharmaceutical company in today's highly competitive marketplace. Many pharmaceutical companies are desperately trying to fill their pipelines as they face decreased revenue due to generics and decreasing internal R&D productivity. There is a clear need for new, innovative compounds, which are quickly becoming a scarce commodity for companies both large and small.

Q: ***What products are currently in development in QuatRx's pipeline?***

A: Our most advanced product candidate is Ophena for the treatment of post-menopausal vaginal syndrome. We recently completed a pivotal Phase III study with Ophena that met all four co-primary efficacy endpoints. We believe the compound holds substantial potential for millions of women in need of alternatives to estrogen to treat vaginal dryness and sexual pain associated with menopause. Until recently, estrogen was broadly used in post-menopausal women, both to treat the initial symptoms of menopause and as a long-term therapy post-menopause. However, following the results of the groundbreaking Women's Health Initiative in 2004, which showed estrogen was associated with certain forms of cancer and myocardial infarction, many women and their physicians now avoid the use of estrogen. Currently, there are no non-estrogen oral treatments on the market to treat menopause symptoms, resulting in a significant treatment gap. The market potential for a non-estrogen therapy in post-menopausal women is substantial.

Our next most advanced program also addresses important issues associated with aging, but in this case, focusing on treatments targeted to men. Fispemifene is an oral, once-daily therapy that addresses a broad range of medical conditions in aging men. Fispemifene normalizes testosterone levels in hypogonadal men via the body's natural feedback mechanisms. Through this action, it should address clinically significant complications of low testosterone, such as erectile dysfunction, strength and agility, anemia, and metabolic syndrome. We have completed a Phase II study that demonstrated a significant (78%) increase in testosterone levels after 4 weeks of treatment. We believe this compound will yield additional benefits in bone preservation and the urinary tract.

Another clinical-stage program is sobetirome, which is targeted at the dyslipidemia market. Sobetirome is a selective thyroid receptor beta agonist, which lowers LDL (bad) cholesterol at least in part by activating steps of reverse cholesterol transport without stimulating thyroid receptors in the heart. We have strong Phase I data with this compound demonstrating LDL cholesterol lowering without changes in heart rate, and preclinical studies and sobetirome's mechanism suggest considerable potential for effects in addition to LDL-lowering, such as reductions in weight, Lp(a) and triglycerides.

Q: ***What business strategies have you taken to enrich your pipeline?***

A: Our entire pipeline has been assembled through acquisition and/or licensing. Our acquisition of Hormos Medical, in particular, has been a key factor in advancing our pipeline, as it resulted in QuatRx acquiring both Ophena and fispemifene, along with our preclinical programs and substantial expertise. The combination of Hormos and QuatRx in 2005 was a pivotal event, and one that we believe has worked out exceptionally well for both companies. The integration of the organizations has been very smooth, and the complementary skill sets have resulted in a company that functions efficiently and professionally.

Q: ***What are you looking for when it comes to partnership opportunities?***

A: QuatRx is in the unique position of retaining all rights to our three key clinical programs in the major markets and of being well funded to carry each program through to clinical proof-of-concept and beyond. We will likely not take all our programs to the market ourselves, so will certainly need partners at some point. However, we have substantial flexibility on when we choose to enter into partnerships with collaborators with each development program. It is quite possible that we will decide to take one or more of our programs to the market ourselves. Our lead program, Ophena, is the ideal compound for this should we wish to develop a commercial infrastructure. The compound would be primarily targeted at Ob-Gyns, a fairly focused physician audience that could be managed with a specialized sales force. These are key decisions that our management team will need to make throughout the coming year.

Q: ***You recently secured a substantial round of financing. What makes the company attractive to VCs?***

A: QuatRx has demonstrated a consistent ability to raise capital from top-tier venture capital firms. Initially, this was a result of the strength of the founding team. As the company has progressed, the breadth and quality of our pipeline have been equally impressive to investors and others. It's been a great asset to have such quality VCs as Frazier Healthcare Ventures, TL Ventures, MPM Capital, Interwest Partners, Kearny Ventures, and most recently, Venrock, associated with the company and providing us with guidance on the board of directors.

Q: ***What unique challenges do you face as a smaller Specialty Pharma company?***

A: Despite being well-funded, we are still a small company and do still need to make choices about allocation of resources. We believe this unique challenge has ultimately benefited the company as it has forced us to be thoughtful about the best way to answer questions and design our clinical studies. There are always additional questions we would like to answer if we had unlimited resources.

Q: ***What is the one mistake you must avoid going forward?***

A: We want to be very careful that any partnerships we enter into are with collaborators who share our focus and vision. As a company that has experienced substantial growth in a relatively short period of time, we want to ensure that we continue to progress our clinical pipeline and grow as a company in a way that benefits all of our stakeholders. ■

We'll take you **there.**

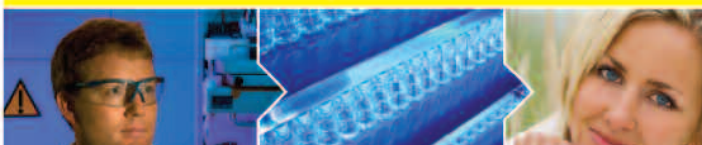
VISIT US AT
BIO
SAN DIEGO JUNE 17 – 20
Booth #218
www.dsmpharmaceuticals.com

API Manufacturing | Clinical Manufacturing | Dosage Form Manufacturing | Scale Up

DSM Pharmaceutical Products

DSM

info.dsmpharmaceuticals@dsm.com 973.257.8011



Therapeutic Markets

Lucrative Therapeutic Markets: Opportunities, Challenges & Future Outlook

By: Barath Shankar Subramanian, Industry Analyst, Pharmaceuticals & Biotechnology, Frost & Sullivan

Introduction

The pharmaceutical and biotechnology industries are in a rapid state of flux. Faced with severe challenges in "traditional therapeutic areas," companies are constantly looking for avenues of growth. This is reflecting on the realignment of growth strategies by most Big Pharma and Specialty Pharmaceutical companies toward areas within specialty and niche pharmaceutical markets that have been significantly under-penetrated and represent a lucrative therapeutic market opportunity.

Lucrative therapeutic markets can be classified into two major types: large multi-billion dollar a year (> $10 billion) markets with low rate of growth (5% to 10%), and smaller multi-million/billion dollar a year (< $10 billion) markets with a high rate of growth (15% to 25%).

While the former represents the "once popular" blockbuster business model, the latter represents the niche/specialty pharmaceutical business model that is becoming increasingly popular with the industry. Some of the lucrative therapeutic markets are: pulmonary arterial hypertension (PAH), opioid and non-opioid pain management, and multiple sclerosis (MS).

Figure 1 shows the revenue share forecasts for the presented lucrative therapeutic markets between 2006 and 2013. The three markets together are forecast to grow from almost $10 billion in 2006 to a little more than $20 billion at a CAGR of 10.7%. This represents a huge growth opportunity for Big Pharma, Specialty Pharma, and Biotechnology companies at a time when there is significant pressure on traditional areas from generics and thinning pipelines.

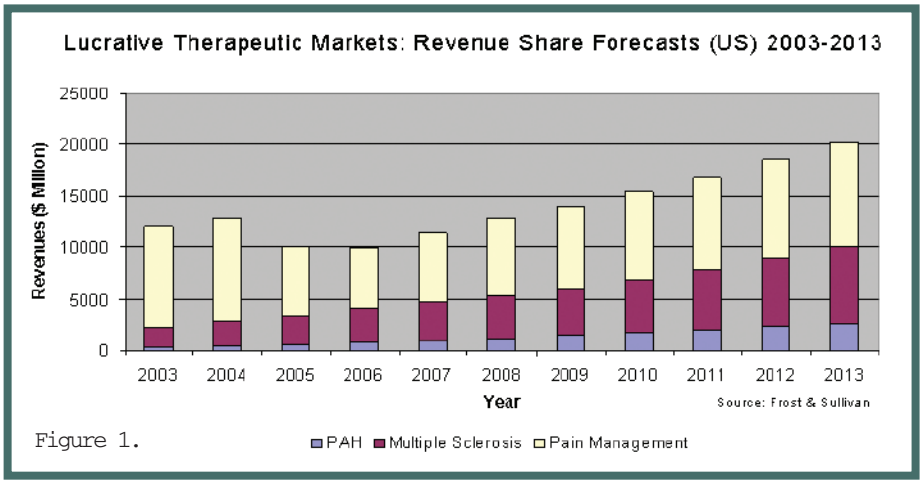


Figure 1.

The key to the success of companies in lucrative therapeutic markets is their ability to innovate and partner. These are market areas that lie beyond the traditional paradigm of pharmaceuticals and are usually ignored by the original developer due to limited revenue potential (< $500 million). Successful Specialty Pharmaceutical companies have been able to partner with drug delivery companies to bring to market newer and improved delivery platforms for their drugs, resulting in new therapeutic opportunities.

Another key aspect that differentiates companies that are successful in smaller, specialty markets is the operational agility, which is further enhanced through partnerships. This is something that Big Pharma companies are increasingly looking toward to be more successful in niche markets.

Pulmonary Arterial Hypertension

Pulmonary arterial hypertension is a rare and frequently terminal condition that afflicts more than 200,000 patients globally. PAH can be inherited, caused by

unknown factors, or occurs due to a pre-existing condition. It is classified as an orphan disease. The market for PAH drugs is forecast to grow from $783.5 million in 2006 to $2.69 billion in 2013 at a CAGR of 19.3%. This is a rapidly growing market, which is attracting significant attention from several companies in the pharmaceutical and biotechnology industries despite its small size (< $800 million). One of the main reasons for the rapid growth of this market has been the potential to repurpose existing drugs for use with a very high unmet medical need. PDE5 inhibitors, which are presently used for the treatment of erectile dysfunction, are emerging as a very effective treatment for PAH.

PAH is a two-tiered market with Big Pharma and Specialty Pharmaceutical companies. There has been an increase in interest from Big Pharma companies due to the growth potential for this market and the fact that Big Pharma companies market most erectile dysfunction drugs.

The PAH market is a classic example of a market with a very small revenue size that is attracting significant interest from across tiers of competition due to its immense growth potential. Traditionally, markets with revenues of $1 billion or lower have been outside the radar of Big Pharma companies, but due to the growth potential and limited competition that exists within these niche markets, there is significant interest from companies that normally wouldn't seek to operate in these areas.

Opioid & Non-Opioid Pain Management

Pain is the most common symptom of injury and disease and can range in intensity from a mere ache to unbearable agony. The US pain management markets are highly dynamic, owing to the widespread prevalence of pain among the population. The cost implication of pain (direct and indirect) is estimated to be more than $100 billion annually with more than 50 million lost workdays. This market is forecast to grow from $5.9 billion in 2006 to $10.17 billion in 2013 with a CAGR of 8.1%.

While Specialty Pharmaceutical companies dominate the opioid pain management market, the non-opioid market has attracted competition from all tiers of the pharmaceutical and biotechnology industry, with Big Pharma companies dominating in terms of revenue and market share. The pain management market is also an area in which there are companies that seek to brand themselves in alignment with the therapeutic area. Examples of this include Endo Pharmaceuticals and Purdue Pharma, which have closely associated themselves with pain management.

Multiple Sclerosis

The US MS markets are entering a new phase of growth driven by the development of innovative therapeutic platforms. A high rate of reimbursement and significantly high potential for market penetration is spurring interest in a variety of companies. The MS market is forecast to grow from $3.25 billion in 2006 to $7.3 billion in 2013 with a CAGR of 12.3%. MS is one of the fastest growing markets for biopharmaceuticals, and the huge unmet medical need has prompted several Big Pharma companies to develop innovative small molecules for the treatment of MS. This stems from the demand for oral therapies with a better side effect profile compared to existing drugs that are mostly injectables with poor side effects.

Summary

As the competition in traditional blockbuster markets continues to grow and generics take up increasing prescription share, specialty and niche markets will become more lucrative for companies to invest in. Big Pharma companies are already modifying their business models to leverage this opportunity.

Smaller markets with significant unmet medical need that have the potential for a premium pricing are expected to drive future market growth and result in increasing strategic partnerships between different tiers. Additionally, drug delivery companies will continue to play an important role in life cycle management and help in providing strong support to innovation. ◆

Mr. Barath Shankar Subramanian

Industry Analyst
Frost & Sullivan North American Healthcare Practice

Mr. Barath Shankar Subramanian is an Industry Analyst with the Frost & Sullivan North American Healthcare Practice. He focuses on monitoring and analyzing emerging trends, technologies, and market behavior in the pharmaceuticals and biotechnology industries in North America. Since joining Frost & Sullivan in October 2004, Mr. Subramanian has completed several research studies and consulting projects on Pharmaceuticals and Biotechnology. Prior to this, he was a Research & Development intern at IPCA Laboratories Ltd., Mumbai, India. He brings with him considerable analytical and quantitative experience, giving him a keen perception into the functioning of technology in the healthcare industry. Mr. Subramanian has received acclaim for his research through articles and quotes published in *Specialty Pharma* and *Drug Delivery Technology* magazines.

Product Development

Which Way to Drug Approval?

By: Stuart Madden, PhD, Senior Vice President of Product Development Consulting & Non-Clinical Services, ICON Development Solutions

Introduction

Which way to drug approval you may ask? Why, the quickest of course! This may seem to be the obvious answer; however, the appropriate (but not the better) answer is: "it depends…"

Routes to approval can include constraints from timing, resources (internal and external), funding and costs, indications sought, regulatory hurdles and technical issues from manufacturing, etc. Typically, several of these factors require consideration when developing a drug product, and ultimately, it is a compromise between competing elements that sets the final development pathway. Thus, it is not always the quickest. The plan is not static either. These influencing factors change throughout the product's development lifetime, sometimes as a result of the program itself (eg, unanticipated data, good and bad) and sometimes from external factors (eg, unexpected competition in the market, unforeseen regulatory change due to market experience with a similar class compound, etc).

A Rational Development Plan

Regardless of the constraints detailed above, the development of any drug product should be viewed in terms of the business. A Product Development Plan is a valuable business tool in this respect. Understanding the costs, timings, scientific challenges, and regulatory hurdles to approval provide visibility to both the scientific and commercial sides of the business, allowing budget management and risk assessment for each key stage of the program.

Typically, product registration is the goal of the development program. For some programs, it may be the validation of a technology platform either by a successful proof-of-concept (PoC) study or by the approval of a drug using the technology platform. In the former case, PoC is the goal; in the latter, it is product approval. Overall product development objectives vary and depend on the company's business objectives. An indication might be viewed as secondary importance to the technology platform.

The drug product should provide some demonstrable benefit over the current standard of care from both an approval (ie, regulatory) standpoint and from a commercial point of view, especially with respect to the marketing aspects for a new technology platform. Understanding the full development program is germane to the company's ability to develop, partner, raise capital, or sell on the asset at a given stage in the program.

The overall strategy employed in developing new products can also be applied to lifecycle management strategies. Effective strategies in product lifecycle management can substantially increase a branded drug's revenues by additional exclusivity. These strategies could be the addition of a new indication, improvements in bioavailability leading to lower dosing and improved safety profiles, moving to a more convenient dosing regimen (eg, three times to once-daily) or changing the route of administration (eg, switching from a nasal spray to an oral tablet or from an oral tablet to a transdermal patch) for improved patient compliance and convenience.

With all of these confounding and interdependent factors, it is clear that there are multiple paths along which a product can be developed. Companies must sift through their priorities to develop a rational strategy to product development. The result is a Product Development Plan that details the requirements from all major scientific disciplines that interact throughout the course of a product's development to take it to registration in keeping with the key objectives of the business.

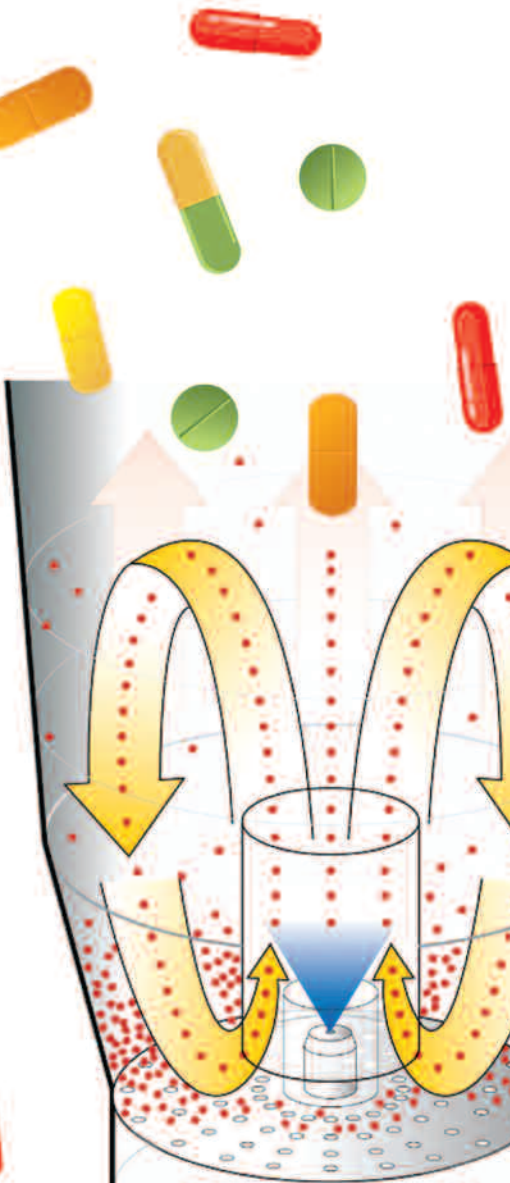
Before developing a Product Development Plan, it is important to understand the company's overall business objectives for the program, which may include the following:

Contract Modified Release Development & Manufacturing from Glatt!

- Glatt Wurster HS™ Pelletizing & Coating
- Glatt CPS™ Pelletizing
- Glatt Fluid Bed Granulation & Drying
- Glatt High Shear Granulation
- Organic Solvent Processing
- DEA Controlled Substance Capability
- From R & D to Commercial Capacities
- Unrivaled Expertise & Customer Care

Glatt Pharmaceutical Services specializes in the development and cGMP manufacture of difficult-to-craft modified and immediate release solid dosage products and is the global leader in fluid bed related product formulation, processing technology and full scale commercial manufacturing.

To learn more, contact us to schedule a visit with our accomplished staff at our newly expanded facility.



Glatt®
Pharmaceutical Services
A Division of Glatt Air Techniques, Inc.

Ramsey, New Jersey
www.glattpharmaceuticals.com
201.825.8700

Delivering Solid Experience

- NDA submission and approval
- Successful PoC study in target indications/populations
- Demonstration of suitable PK profiles in healthy volunteers
- Opening of an IND

Whether they are short-term (opening of an IND) or long-term (NDA approval), all will benefit from a Product Development Plan.

Target Product Profile

The Product Development Plan can be thought of as a road map that will enable the business to understand what routes are available to take the program from its current point to submission. The most important part of this road map is actually the destination. The destination can be defined as the Target Product Profile. The Target Product Profile can be viewed as a format for describing all the key aspects of the product in terms of labeling concepts. At the early stage of development, it is not possible to populate all aspects of the Target Product Profile in full. Three labeling concepts of the Target Product Profile that should start to be defined at an early stage are: Indications and Usage; Dosage and Administration; and Dosage Forms and Strengths. It may appear premature to start thinking about these details at the very early stages of a program as they are probably the last items to be agreed upon and finalized by the regulatory agency. Defining the indications, usage, dosage, and administration helps:

- Initiate thinking on establishing the drug product's potential efficacy and safety relative to the current standard of care.
- Begin the process of understanding the extent (number of patients and duration) of the pivotal clinical program. This would be important from an overall financing perspective (especially for smaller or emerging pharma).
- Identify the competition (ie, how it is likely to be assessed during the clinical program).
- Provide a clear understanding of the market(s).
- Determine the information that needs to be developed for care providers to use the drug properly.

Answering these questions will also drive an understanding of requirements with respect to dosage forms and strengths that will enable a truly focused formulation development program.

The Advantages of a Development Program

With an understanding now developed in these key areas, the preclinical requirements to support each phase of the development program become further defined, and the data that will be required to meet the regulatory requirements at each stage of the program become clarified.

Beginning to define these areas also shows the opportunities for a fast-track regulatory path (for treatment of a serious or life-threatening condition or the potential to address an unmet medical need) leading to accelerated approval (via a rolling submission) or the opportunity to obtain orphan drug approval.

Summary

In summary, the ultimate goal of a Product Development Plan is to ensure that the correct research is performed to determine whether a drug is safe and effective for clinical use. The final result is that the correct information is obtained during the development program to allow the optimal use of the drug for a given patient. A Product Development Plan is a living document that changes given the data obtained, new science, the regulatory environment, the competition, sales/marketing goals, and the goals of the business. ◆

Stuart Madden, PhD, FRSC,

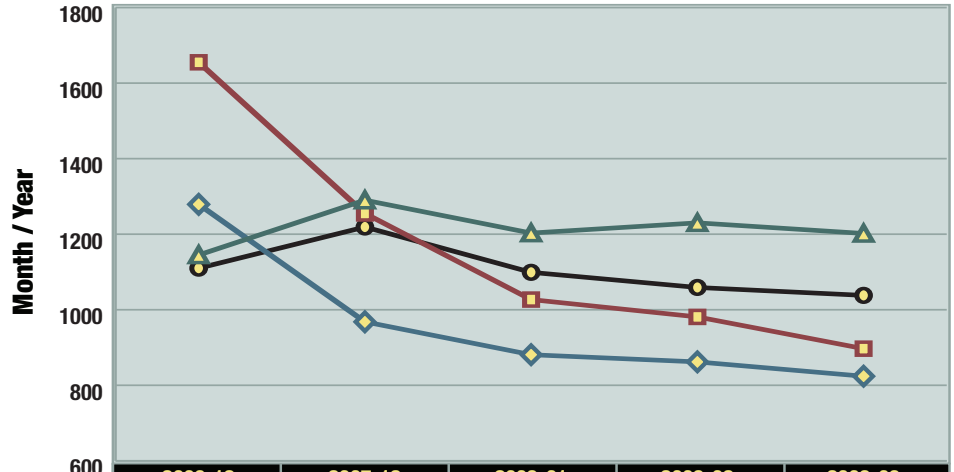
Senior Vice President, Strategic Drug Development & Non-Clinical Services ICON Development Solutions

Dr. Stuart Madden is Senior Vice President of Strategic Drug Development & Non-Clinical Services, responsible for the management of ICON's Strategic Drug Development, CMC and Preclinical scientific teams. He has over 20 years in the pharmaceutical industry working on drug development, from proof-of-concept through to commercialization. His experience in both research and manufacturing settings has provided him with ample background in addressing the challenges in bringing a product to submission. Dr. Madden earned his BS in Chemistry and his PhD in Physical Chemistry from the University of Wales, UK. Dr. Madden then spent 2 years as a Post-doctoral Fellow at San Diego State University, California. His PhD and Post-Doctoral research focused on modelling adsorption mechanisms in high-performance liquid chromatography systems. He has held a number of positions with several international pharmaceutical companies (primarily within research and development), has experience in commercial manufacturing, has published in the areas of adsorption mechanisms in HPLC, novel degradation chemistry in formulated products, has contributed to texts on in vitro/in ivo correlations, and is a Fellow of the Royal Society of Chemistry. Prior to joining Development Solutions, Dr. Madden was Senior Director of Analytical Sciences for the Elan Corporation, specializing in the development of modified-release solid oral dosage forms from conception through NDA submission to commercialization.

Facts & Figures

For index methodology and more detailed analysis please visit www.bionumbers.com

Bionumbers Composite Index



*The indexes refer to Market Capitalization rather than Share Price

	2006-12	2007-12	2008-01	2008-02	2008-03
CSPI	1,145	1,290	1,203	1,230	1,202
ESPI	1,655	1,255	1,027	981	897
DDI	1,279	968	881	862	824
NASDAQ	1,110	1,219	1,099	1,059	1,038

Index Value

CSP Index Value: 1202 | Change YTD: -6.8% | Change M/M: -1.8% | Total Index Capitalization: $53.2 Billion

Top 5 Capitalizations YTD Change		
Shire	$11.7 Billion	-9%
Hospira	$6.8 Billion	+2%
Warner	$4.3 Billion	-4%
Perrigo	$3.5 Billion	+8%
Endo	$3.1 Billion	-13%

Top 5 Gainers YTD Change	
Millbrook	+312%
Encysive	+179%
Collagenex	+74%
Dusa	+17%
Draxis	+14%

Top 5 Laggards YTD Change	
Ista	-54%
Angiotech	-47%
Indevus	-36%
Repligen	-32%
Alkermes	-30%

ESP Index Value: 897 | Change YTD: -28.5% | Change M/M: -10.0% | Total Index Capitalization: $2.5 Billion

Top 5 Capitalizations YTD Change		
Nektar	$614 Million	-1%
Durect	$372 Million	-22%
Pain Therapeutics	$365 Million	-22%
Cadence	$225 Million	-48%
Alexza	$215 Million	-14%

Top 5 Gainers YTD Change	
NovaDel	+29%
Catalyst	+7%

Top 5 Laggards YTD Change	
Keryx	-93%
Elite	-61%
Epicept	-55%
Cadence	-48%
Acusphere	-44%

DD Index Value: 824 | Change YTD: -14.9% | Change M/M: -7.6% | Total Index Capitalization: $9.3 Billion

Top 5 Capitalizations YTD Change		
Biovail	$1.9 Billion	-15%
Alkermes	$1.1 Billion	-30%
Surmodics	$732 Million	-27%
Eurand	$662 Million	-4%
Nektar	$614 Million	0%

Top 5 Gainers YTD Change	
Labopharm	+101%
Acura	+61%
Momenta	+48%
NovaDel	+29%
Inovio	+18%

Top 5 Laggards YTD Change	
Vyteris	-77%
Elite	-61%
CytRx	-58%
Generex	-44%
Acusphere	-44%

Changing Business Practices in the Chinese Pharmaceutical Market

By: Ames Gross, President & Founder, and John Minot, Associate, Pacific Bridge Medical

Introduction

For pharmaceutical companies in China, today is a very exciting time, but also a highly challenging one. Thanks to a rapidly rising economy (GDP growing more than 11% in 2006) and newly prosperous citizens wanting better healthcare, the pharmaceutical market there is growing quickly, at about 15% per year. In 2010, some experts predict that China will be the fifth-largest drug market in the world. However, due to demographic and regulatory changes, the market's structure and incentives are shifting rapidly. Some Chinese drug manufacturers are going out of business, while others are changing just to survive. Foreign drug companies continue to have many market advantages for their high-end products, but they will also need to move rapidly to keep this position.

Current Market Structure

The following are the main features of China's current drug market:

- HOSPITAL-BASED: 63% of all drug sales are in hospitals. In general, the bigger the hospital, the greater the per-patient spending.
- HEAVILY URBAN: Per capita health expenditure in urban areas is 3.5 times what it is in rural areas. Traditionally, it is also oriented toward the biggest cities; more than one-third of hospital drug sales are in the top 16 cities alone.

  Multinational corporations (MNCs) have a much greater focus on these cities due to higher income levels there.
- BASED ON SELF-PAY: Although some medical expenses are paid by employers, government, and others, more than 50% still come out-of-pocket. Currently, private health insurance plans almost exclusively cover in-patient care, not prescriptions.
- OFTEN BIASED TOWARD MORE EXPENSIVE DRUGS FOR PATIENTS WHO CAN AFFORD THEM: Although most hospitals are state-owned, a large part of their operating revenue comes from the sale of drugs through in-house pharmacies. Chinese hospitals are only permitted to mark up a drug's consumer price to 15% over the purchase price.

Multinational Versus Domestic Firms

Twelve of the top 20 drug firms in the Chinese hospital market are foreign MNCs, which have a favorable market environment in China for many reasons. Their core advantage is that they have distinguishable, innovative, sought-after products. MNCs are experiencing an average sales growth of about 25%, compared to 15% for the market as a whole. Some key money-making areas for them are cardiovascular health, diabetes, and cancer.

MNCs also often have highly trained sales forces and good relationships with key opinion leaders (KOLs). On average, MNC drug companies spend $200,000 annually on sales force education and training, compared to $50,000 spent by domestic drug firms.

The characteristics of domestic Chinese drug firms are more varied, but they are almost all generic companies. They dominate the local active pharmaceutical ingredient (API) and over-the-counter (OTC) markets, but not the prescription markets. There are both large companies and vast numbers of small-to-medium Chinese manufacturers and distributors across the country. Many of these Chinese companies, as well as some larger ones, are suffering from low profit margins and bad debt.

Regional Demographic Shifts

As mentioned previously, more than one-third of China hospital drug sales are in the top 16 cities today. However, this figure was almost half in 2000. The reason for the decline is that the major coastal cities (Beijing, Shanghai, Guangzhou, etc.) are becoming less economically dominant. As wages rise, many industries are relocating to less-developed "second-tier" cities (Suzhou, Wuhan, Chengdu, etc.). This process is kick-starting economic performance and living standards, leading to increasing numbers of drug consumers in more areas of China.

Because many second-tier cities are further inland than the other major cities, drug consumers are now more geographically diverse. In response, Western manufacturers may need to find distributors for more Chinese regions. If they have their own sales force, they may need to expand their geographical coverage.

Corrupt Practices

Giving kickbacks to hospitals and other purchasers is common in the Chinese domestic drug industry. Some domestic firms have essentially based their sales strategy around it, with sizable budgets for "relationship management." Others, including some foreign drug companies, rely on distributors or independent sales agents to do this for them. However, using kickbacks is not an ideal long-term way of doing business in China due to the government's new efforts to eliminate them.

Previously, there was no effective sanction for corrupt practices. However, due to public outcry over deaths caused by faulty drugs, the government is currently cracking down. It went as far as executing its own top drug regulator at the State Food and Drug Administration, Zheng Xiaoyu, for corruption in July 2007. Many businessmen have also been arrested by stepped-up enforcement, causing concern in the domestic industry. Some large domestic drug companies are now actively formulating long-term strategy shifts that will make them much less reliant on kickbacks and similar practices. MNCs generally have better systems of Western ethics in place already; in addition, they have less need to give kickbacks, due to their unique products.

Drug Reimbursement Issues

Products on the National Reimbursement Drug List (NRDL) commonly have a significant advantage over other drugs that are not on the list. It is true, as mentioned earlier, that much medical care is paid for on a self-pay basis in the Chinese market. However, for patients in the Basic Medical Insurance (BMI) system (about 180 million, most of the urban residents), the government reimburses 70% to 90% of the cost of drugs listed in the NDRL.[1] This leads to patients preferring, or even demanding, a listed drug over others that could be prescribed.

The NDRL is theoretically revised every 2 years, but the last revision was 4 years ago. Also, if BMI patients exhaust their "Individual Account" (an account dedicated to outpatient expenses, co-pays, and drug costs), the patient must pay all drug costs out-of-pocket, without reimbursement.

Typically, when a drug is put on the NDRL, generic competition intensifies. The National Development and Reform Commission (NDRC) also tends to issue price cuts to help control government spending on reimbursement. Together, these processes push down the price over time. It should be noted though that there is still a niche for more expensive original-brand drugs (mostly from MNCs) on the Chinese market, even when there is generic competition. This is because the NDRL lists drugs based on their active ingredient, regardless of price. Therefore, original-brand products receive the same reimbursement as a percentage of price, even though the price may be three to five times higher. Urban hospitals commonly stock them alongside generics for the patients who can afford them.

Possible future reforms to the NDRL include: 1) liberalizing the process of listing drugs for reimbursement; 2) reimbursing based on a generic price (not as a percentage of the actual price, regardless of how high it is); and 3) limiting annual drug reimbursement per patient. These would have different impacts on the industry. Liberalizing the entry of drugs onto the reimbursement list would help the producers of newly entering drugs, domestic and foreign. On the other hand, reducing reimbursement of more expensive listed drugs would remove some of the incentive for hospitals to buy them. Still, in general, wealthier consumers should continue to prefer foreign drugs for their quality.

Hospital Purchasing Issues

Another important change to the drug market in China is greater hospital tendering. More and more, large hospitals are forming purchasing networks to combine their purchasing power. For example, in 2006, the tendering system in Guangdong province (China's largest hospital-drug market on a provincial basis) was able to cut drug prices by an average of 30%. The processes governing hospital tenders are also becoming somewhat more transparent. Depending on the system, bidding prices are often made public, and more tendering systems are also now conducted online. This allows greater access to new entrants with fewer connections.

Currently, hospitals tend to stock one original brand and a few generic brands. However, the recent Ministry of Health (MOH) Order 53, Measures for Prescription Management, restricted hospitals to stock no more than two brands of any chemical substance. In response, hospitals are expected to reduce their stocks to one original brand and one generic brand only. This will put even more pressure on generic prices since

generic manufacturers will have to compete for one slot instead of two.

Healthcare Reform Prospects

In the longer term, some kind of broad reform to China's healthcare system is likely. Some elements of reform under debate include the following:

- a shift from large hospitals to smaller community medical institutions to deliver major care;
- standardization of outpatient fees and total inpatient fees; and
- allowing the NDRC to set prices for most drugs as soon as they come on the market (except patented drugs; for these, the NDRC would merely reserve the right to intervene in pricing).

Even if none of these changes comes about, the government is already expanding membership in the existing public healthcare insurance systems. It plans, very optimistically, to cover all of China by 2010. There is also a good deal of public enthusiasm for the idea of eliminating the mark-ups hospitals charge on drugs altogether. This would remove a large cause of the Chinese medical system's bias toward more expensive drugs. However, it would be extremely difficult to achieve politically unless a new source of hospital income is found to make up the resulting deficits.

Industry Reactions

The drug industry in China is under significant price pressure from the various previously mentioned changes (price cuts, stricter hospital tendering, possible reimbursement cuts, etc.) and should find this pressure rising over time. However, the government's reform measures focus more on generic products than on original or patented products. MNCs' sales growth is higher on average than domestic companies' sales growth and is likely to stay that way due to inherent advantages.

A major strategy that domestic drug companies are taking to combat these pressures is differentiation of products. In a country with a fiercely competitive generic market, standing out in one way or another is understood to be a sales advantage. As a first step, many domestic companies are now marketing novel dose levels or combination products. Other practices include greater branding and marketing, engaging key opinion leaders, in-licensing patented drugs from MNCs, and even developing patented products themselves. At this stage, many of their patented products are Traditional Chinese Medicine (TCM) rather than Western medicine. However, that should change over time.

Opportunities for MNCs are also directly affected by the current trends. In particular, out-licensing a patented product to a Chinese drug firm was unthinkable in the past due to intellectual property concerns. Today, out-licensing may at least be worth consideration.

Summary

In the long-term, Chinese drug firms are being pressured by ongoing market and regulatory changes to become less focused on generics and more like global pharma, trading on differentiation, branding, and innovation. It will be difficult and time-consuming for them to restructure themselves to innovate. If they succeed, MNCs may find themselves with less of an inherent market advantage in China. However, for the time being, China is still an excellent destination for Western pharmaceuticals. ◆

Reference

1. The NDRL is also used by the other major state-run medical insurance systems, including programs for rural residents (a system currently being expanded across the country), the military, and students.

Mr. Ames Gross

President & Founder
Pacific Bridge Medical

Mr. Ames Gross is President and Founder of Pacific Bridge Medical (PBM) and is recognized nationally and internationally as a leader in the Asian medical markets. Established in 1988, PBM is a consulting firm that assists medical companies with business development and regulatory issues in Asia. PBM has helped over 200 medical companies in Asia. Mr. Gross is a frequent contributor of articles on Asian medical issues for *Medical Device and Diagnostic Industry* (Los Angeles), *Clinica* (England), and other medically oriented journals. Mr. Gross is often a featured speaker at the Regulatory Affairs Professionals Society conferences, the Asian medical markets at the Medical Design and Manufacturing shows, the National Electrical Manufacturing Association meetings, and the Medtrade Home Health Care Exhibition, among others. Prior to establishing PBM, Mr. Gross gained broad experience, knowledge, and contacts in Asia while working at three major Wall Street firms. Mr. Gross earned a BA degree, (*Phi Beta Kappa*) from the University of Pennsylvania and an MBA from Columbia University. To purchase his comprehensive report on Orphan Drugs in Asia, please see the *Publications for Sale* section on his website (www.pacificbridgemedical.com).

Mr. John Minot

Associate
Pacific Bridge Medical

Mr. John Minot is an Associate at Pacific Bridge Medical. Mr. Minot has extensive experience working on research and writing projects focusing on various pharmaceutical market segments.

April 2008

Advertiser Index

Company	Pg	Phone	Web Site
3M	5	800-643-8086	www.3m.com/dds
Azopharma	Cover, 4	954-433-7480	www.azopharma.com
BASF	23	800-469- 7541	www.pharma-ingredients.basf.com
BD	33	800-225-3310	www.bdpharma.com
Bilcare Global Clinical Supplies	63	610-935-4300	www.bilcare.com
Capsugel	17		www.capsugel.com
Catalent Pharma Solutions	84	866-720-3148	www.catalent.com
Controlled Release Society	14		www.controllereleasesociety.org/meeting
Davidson, Davidson & Kappel	59	212-736-1940	www.ddkpatent.com
Dow Pharmaceutical Sciences	15	707-793-2600	www.dowpharmsci.com
DSM Pharmaceuticals	71	973-257-8011	www.dsmpharmaceuticals.com
Élan	37	610-313-8867	www.elan.com
Eurand	7	937-898-9669	www.eurand.com
Evonik Degussa Corporation	9	732-981-5383	www.eudragit.com/drugdelivery
Frost & Sullivan	53		www.frost.com
Glatt Pharmaceuticals	75	201-825-8700	www.glattpharmaceuticals.com
InnerCap Technologies	3	813-837-0796	www.innercap.com
Multisorb Technologies	19	716-824-8900	www.multisorb.com
NOF Corporation	83	914-6819790	www.nof.co.jp/dds
Nusil	13	805-684-8780	www.nusil.com
Penwest Pharmaceuticals	29	203-796-3700	www.penw.com
PharmaCircle	47	847-729-2960	www.pharmacircle.com
PharmaForm	11	512-834-0449 Ext 201	www.pharmaform.com
PPD	65	859-442-1300	www.ppdi.com
Soliqs	25	877-765-4771	www.soliqs.com
SPI Pharma	2		www.spipharma.com
Xcelience	21	608-643-4444	www.xcelience.com

EXTERNAL DELIVERY

Greedy-Nomics

By: John A. Bermingham

Awhile back, I wrote an article on the sub-prime mortgage mess. At that time, I had believed like many others that this was a bit over blown by the media. Well, I am here to say that I was wrong. Gosh, it's only March, and I have made my first mistake for 2008! Just kidding Dan-O.

So where did I miss it? Well, everything that I had read up to the time of my article indicated that sub-prime mortgages were only about 10% of all mortgages and only a fraction of those were heading for or were in default. This crisis began with the bursting of the housing bubble causing the value of homes to decline, causing high default rates on sub-prime mortgages, such as adjustable rate mortgages (ARMs). High-risk and low-income earners were given incentives to take out sub-prime loans that would allow them to buy homes that they normally could not afford. Unfortunately, these borrowers ended up in an upside down position, that being that their mortgage balances were higher than their homes were worth, and refinancing was out of the question. That began the foreclosure boom. The *Economist* magazine estimated that sub-prime defaults would reach a level between $200 to $300 billion in the US.

Mortgage lenders were negatively affected, major banks and financial institutions began reporting losses in the billions, and third-party investors who had investment vehicles in these mortgages then took a substantial hit as the underlying mortgage assets declined. Then the stock markets in many countries began to decline. Then the US economy began to suffer the effects. The domino effect in full play!

So who is to blame for this mess? The people who borrowed over their heads on their home mortgages and ended up not being able to make their payments or to refinance to a lower payment? In my opinion, absolutely not! This was pure greed on the parts of the banks, mortgage brokers, and *Wall Street*.

For example, bankers wagered their banks' capital (not their own personal capital of course) on a bet that if everything went right in the sub-prime housing market, they would receive millions of dollars in bonuses. If they lost on this bet, then it became the shareholders' problem. Thanks a lot! Result: bulge bracket banks, such as Merrill Lynch to Citigroup, wrote off billions of dollars, their CEOs lost their jobs, albeit leaving with tens of millions of dollars in severance packages, Bear Sterns collapsed, and thousands of people are now without jobs. Don't be surprised when you read that these former titans of finance are now partners in private equity and venture capital firms making more millions of dollars.

Why my tirade? Because so many of our citizens' homes have been foreclosed upon or are about to be due to the mess that was caused by the self-centered greedy decisions of the financial world. Our citizens now have major financial problems. I won't even bring up the effect this has had on our economy and stock market. Hence, the negative financial effect this has had on all of us. They took advantage of people who saw the opportunity to buy their first home, told they could refinance later to a lower rate of payment, and all would be wonderful. Did anyone bother to explain the risk to these people? I think not! Greedy-Nomics at its best! ◆

BIOGRAPHY

John A. Bermingham is currently the President & CEO of Lang Holdings, Inc., an innovative leader in the social sentiment and home décor industries. He was previously the President, Chairman, and CEO of Ampad, a leading manufacturer and distributor of office products. With more than 20 years of turnaround experience, Mr. Bermingham also held the positions of Chairman, President, and CEO of Centis, Inc., Smith Corona Corporation, and Rolodex Corporation. He turned around several business units of AT&T Consumer Products Group and served as the EVP of the Electronics Group and President of the Magnetic Products Group, Sony Corporation of America. Mr. Bermingham served three 3 in the U.S. Army Signal Corps with responsibility for Top Secret Cryptographic Codes and Top Secret Nuclear Release Codes, earned his BA in Business Administration from Saint Leo University, and completed the Harvard University Graduate School of Business Advanced Management Program.

Worldwide leader in DDS

NOF CORPORATION provides outstanding quality, innovative drug modifiers, carriers and emulsifiers. NOF has an exellent reputation producing these products in their cGMP facilities.

Activated PEGs

- Outstanding Quality PEGs and Activated PEGs
- Narrow Polydispersity & Low Diol content
- cGMP production
- New Branched PEGs and Multi-arm PEGs

NOF Activated PEG

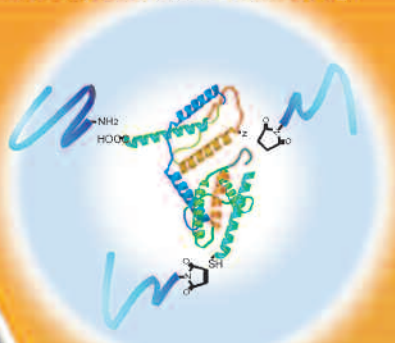
GPC Chart

Low Polydispersity: Mw/ Mn = 1.03
Low diol content

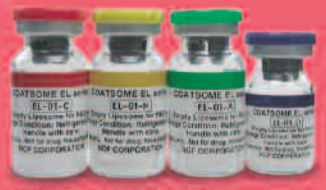
New GMP Plant
&
DDS R&D

PEGylation

- Wide Range Selection of Activated PEGs
- Advanced PEGylation Technology
- PEGylation of protein, peptide, nucleic acid, etc.
- Prolonged blood circulation of the Drug



PEG-DRUG

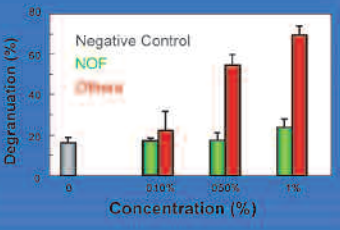


Empty-Liposome Kit

- Outstanding Quality & GMP production
- Numerous Drug Master Files
- Ready-to-use freeze-dried liposome kit
- PEGylated & Targeting Liposome Technology

Phospholipids and Liposome

NOF Others



- Outstanding Quality
- Multi-Compendial NF, EP, and JP
- Low Impurities and Peroxide
- Low Toxicity & Hemolysis
- Low Degranulation (Low Allergic Reaction)

Ultra-pure Polysorbate 80

NOF CORPORATION

DDS Development Division
Yebisu Garden Place Tower
20-3,Ebisu 4-Chome
Shibuya-ku, Tokyo 150-6019 JAPAN

http://www.nof.co.jp/dds/ E-mail: ddsinfo@nof.co.jp
Tel:+81-3-5424-6741 Fax:+81-3-5424-6769

NOF America Corporation
One North Broadway, Suite 1012, White Plains, NY 10601, USA
TEL: +1-914-681-9790 FAX: +1-914-681-9791
E-mail: info@nofamerica.com

NOF Europe (Belgium) NV
Bouwelven 1, Industriezone Klein-Gent, B-2280 Grobbendonk, Belgium
TEL: +32-14-230001 FAX: +32-14-224563
E-mail: hilde.peelaerts@nofeurope.com

Where Drug Development, Delivery, Manufacturing and Packaging converge.

There is a point where everything comes together. Where creativity and talent intersect with experience and capability. Where you can move forward with security and confidence.

For years, Catalent Pharma Solutions has been at the vertex of the industry, providing innovation and operational excellence across the supply chain. With our proprietary technologies, expertise and global infrastructure, we can be a catalyst for your products' success from development straight through to commercialization.

With Catalent, you will find the services you need to get your products to market faster. *That* is the point of best returns.

For more information, contact us at +1 866 720 3148, email us at sales@catalent.com, or visit www.catalent.com.

Catalent

Reliable Solutions. Inspired Results.™