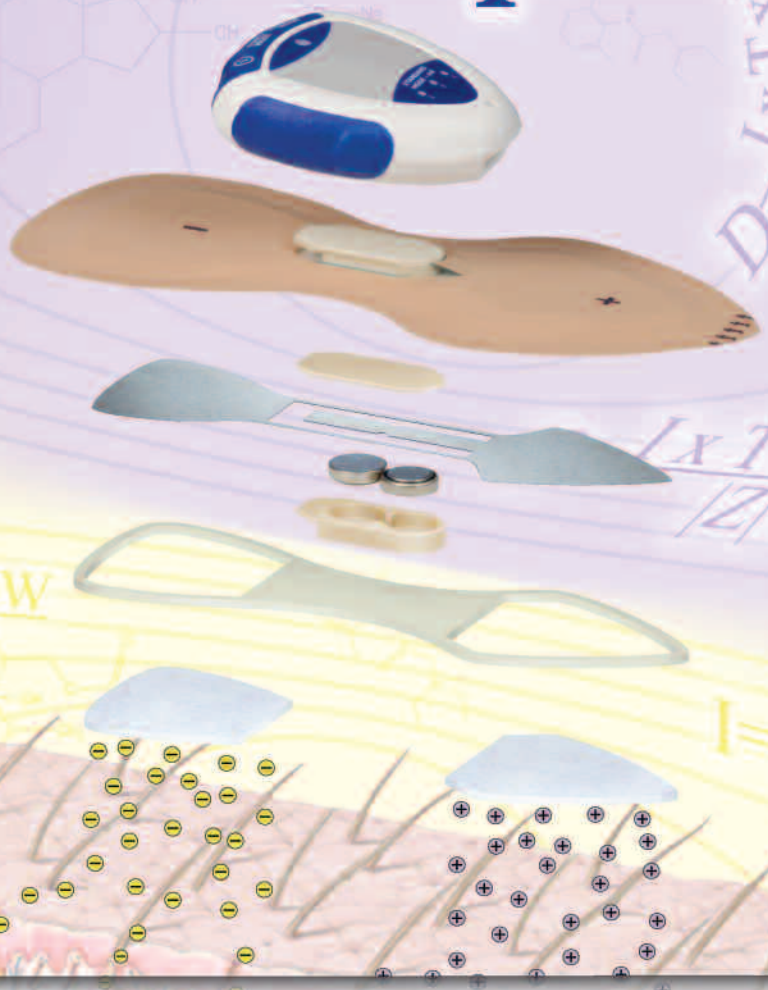
Drug Delivery® Technology

April 2007 Vol 7 No 4 www.drugdeliverytech.com

Hybridizing Iontophoresis



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

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- cGMP production
- New Branched PEGs and Multi-arm PEGs

NOF Activated PEG

GPC Chart

Low Polydispersity: Mw/ Mn = 1.03
Low diol content

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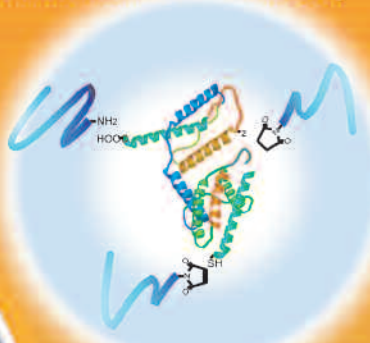
&
DDS R&D

PEGylation

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



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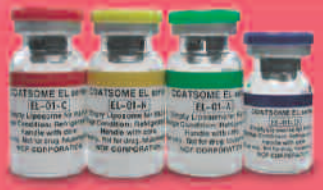

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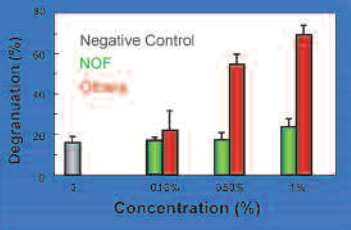
Phospholipids and Liposome

NOF Others



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THE ADVANTAGES

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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.

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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.

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

Unique Appearance
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Compounds
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Patent Pending US-2005-0008690-A1

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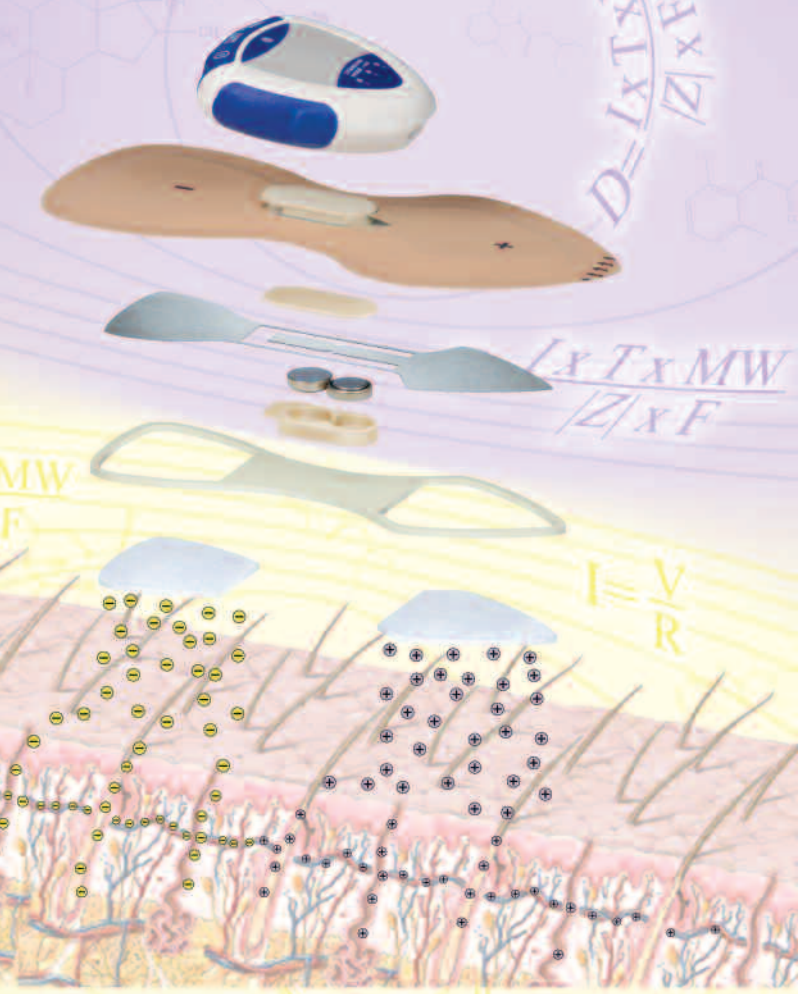
Transdermal Iontophoretic Delivery



"The Hybresis™ System was designed predominantly for use in the physical therapy market. However, its miniaturized, wireless dose controller directly connected to the integrated transdermal patch lends itself to development of drug-specific iontophoresis delivery systems for the pharmaceutical industry."

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Unparalleled taste Flexible dose Versatile release Robust tablet

AdvaTab® The next generation ODT

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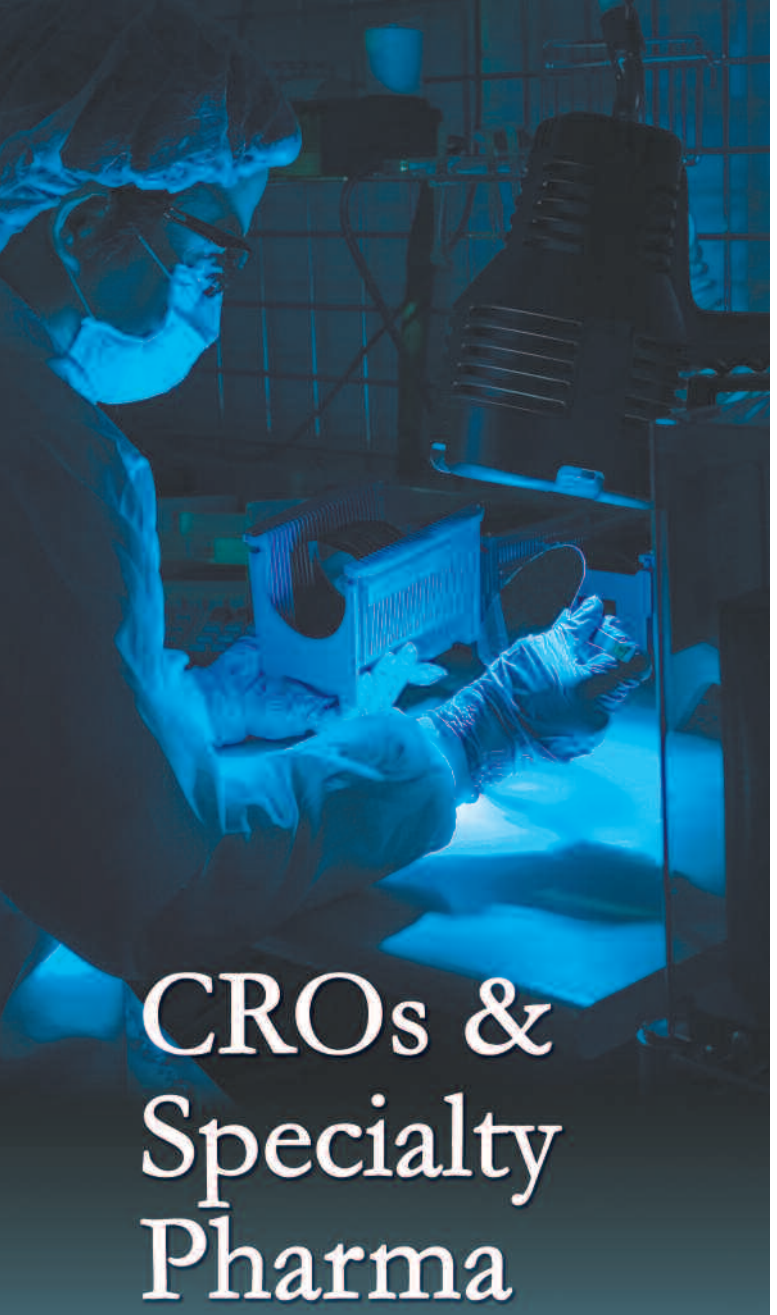

CROs & Specialty Pharma

"Outsourcing to CROs by pharmaceutical and biotechnology companies continues to be a growing trend with more than 20% of cardiovascular and oncology clinical development currently being outsourced, according to market research analysts at Frost & Sullivan. Additionally, therapeutic areas, such as metabolic diseases, are likely to be increasingly outsourced in the next 12 to 24 months."

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Departments

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Market News and Trends

Dow & Colorcon Join Forces in Bringing Excipients for CR Applications to the Pharmaceutical Market

The Dow Chemical Company recently announced an alliance with Colorcon, Inc. for the global marketing, sales, technical service and development, and distribution of Dow pharmaceutical excipient products for use in controlled-release applications. The agreement applies to select Methocel™ hypromellose polymers, Ethocel™ ethylcellulose polymers, and Polyox™ poly(ethylene) oxide resins.

This global strategic alliance amplifies both companies' offerings to the pharmaceutical market by fusing Dow's expertise in excipient technology with Colorcon's leading position in drug dosage formulation. Controlled-release excipients provide the benefits of consistent drug release over time. The collaboration between Dow and Colorcon will bring more technologically advanced excipients to more drug manufacturers worldwide.

"The alliance between Dow and Colorcon is a natural outcome of a 28-year-old cooperation between the two companies and our answer to the global pharmaceutical industry's demand for faster development and more efficient production of drug ingredients," said Philip Pilnik, Commercial Director for Dow Pharmaceutical Excipients. "By formally joining Dow's expertise in polymer science and technology development with Colorcon's global infrastructure, application development, and customer service experience, we are able to create a more valuable – and easily accessible – resource for our pharmaceutical customers, who are increasingly global in their operations."

Jim Coward, Vice President and General Manager for Colorcon Modified Release Technologies, added, "We see this global alliance as a natural progression for both companies in providing increased value to the pharmaceutical formulator. Our goal is to provide a full range of products, tools, and services for modified-release application in tablet, multi-particulate, and osmotic formulations. By expanding our relationship with Dow, we expect to accelerate our new product development efforts, as well as improve existing solutions for controlled release."

As a result of the alliance, Dow and Colorcon expect to further develop the market for Methocel, Ethocel, and Polyox resins for controlled-release applications. Additionally, distribution of select Methocel, Ethocel, and Polyox resins for controlled-release applications will be transitioned to Colorcon from Dow's existing distributor network. Conceived with the pharmaceutical customers in mind, this exclusive global alliance will facilitate all phases of choosing and sourcing excipients, from initial technology development through final commercialization and product delivery – all through a single contact point.

"Dow's current customers will benefit from a consistent and more valuable supply chain," said Marty Kollmeyer, Business Director for Dow's Methocel polymers. "Further, because the global alliance promotes the most efficient use of resources, we will be able to focus our efforts on building on our polymer science capabilities to accelerate innovation and speed-to-market – underscoring our commitment to provide the pharmaceutical market with tailored solutions."

Bill Motzer, President and CEO of Colorcon, added "This alliance with Dow furthers Colorcon's commitment to the global pharmaceutical industry. Our goal is to be an extension of our customers' product development team, from formulation design to scale-up. We will continue investing in our key platforms and global infrastructure to meet our customers' changing needs."

Eisai to Acquire Morphotek, Makes Leap Toward Biologic Therapeutics

Eisai Co., Ltd., Eisai Corporation of North America (ECA), and Morphotek Inc. recently announced that ECA has signed a definitive agreement to acquire Morphotek for $325 million after excess net cash.

Morphotek develops therapeutic monoclonal antibodies through the use of proprietary human antibody technologies, including Human Morphodoma and Libradoma. The company is leveraging these technologies to enrich its pipeline that already includes therapeutic antibody leads for the treatment of cancer, rheumatoid arthritis, and infectious disease. Two of its programs are currently in early stage clinical trials for the treatment of ovarian cancer and pancreatic cancer, respectively, with several others in preclinical development.

Eisai currently has an extensive global oncology research program for discovering small molecule anti-cancer agents, and upon completion of the acquisition, will expand its capabilities into the biologic therapeutics field. With this unique and strategic antibody technology acquisition, Eisai can meet a variety of medical needs of cancer patients, through the development of therapeutic antibodies, small-molecule anti-cancer drugs, and potential combinations of both.

"I sincerely respect Morphotek's CEO, Dr. Nicholas Nicolaides', innovative and courageous endeavor in developing human monoclonal antibody therapeutics," said Mr. Haruo Naito, Eisai's President and CEO. "He has made a tremendous contribution to that effort. By combining Morphotek's proprietary technologies and promising therapeutic antibodies with Eisai's existing research programs and infrastructure, we will be able to meet our goal of addressing the unmet medical needs of patients, especially cancer patients, all around the world. Morphotek's rich pipeline, unique and proprietary antibody generation technology platform, and highly skilled management and scientific team will become the core of our R&D efforts in biologics."

Dr. Nicolaides said, "Eisai's substantial intellectual and managerial resources will enable us to accelerate the development of our current therapeutic antibody pipeline as well as develop a number of additional clinical compounds to targets accessed from our broad network of research collaborations and to those discovered by Eisai researchers globally."

Upon completion of the transaction, Morphotek will become part of Eisai's growing global discovery and development research network, which is composed of research laboratories in Japan, Europe, and the US. The addition of Morphotek further extends Eisai's research presence in the US, which includes the Eisai Research Institute of Boston, Inc., a discovery operation based in Andover, Massachusetts; Eisai Medical Research Inc., for clinical development, located in Ridgefield Park, New Jersey; and RTP laboratory for formulation research in North Carolina.

"Morphotek will enjoy its autonomy in Eisai's discovery network, but I will encourage close collaboration among all Eisai R&D member companies. We very much look forward to welcoming Morphotek to the Eisai family of companies," concluded Mr. Naito.

This planned expansion of Eisai's discovery, research, and clinical capabilities complements Eisai's establishment of its oncology sales and marketing operations in the US under ECA. Aided in part through its recent acquisition of four oncology-related products from Ligand Pharmaceuticals in October 2006, which included the retention of key oncology personnel and expertise, including a sales force, Eisai has developed its commercial oncology infrastructure and is well positioned to market new oncology products that originate from Eisai's research and discovery efforts or through future acquisition, co-promotion, or in-licensing opportunities.

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Hovione Licenses Inhaler Technology for Influenza Drug to Sankyo & Biota

Hovione recently announced the signature of an agreement in which Sankyo Company Ltd. and Biota Holdings Ltd. have jointly licensed Hovione's dry powder inhaler technology for the delivery of long-acting neuraminidase inhibitors (LANI) owned by Sankyo and Biota, which are active against the influenza virus. An improvement over other approved medicines that have to be taken repeatedly is that this novel compound is expected to remain active for several days and require to be taken once only. Hovione retains all inhaler rights outside the field of influenza.

Under the agreement, Hovione has developed a low-cost disposable inhaler, TwinCaps, specifically for this indication. In addition, Hovione carried out inhaler compatibility studies and comprehensive formulation development to demonstrate that the lead clinical candidate CS-8958 can be delivered by inhalation. Sankyo and Biota are responsible for the clinical development of the drug product, which is expected to start in the near future. CS-8958 has already completed Phase I clinical trial in a prototype inhaler.

Peter Villax, Hovione Vice-President, said, "This agreement is the confirmation that Hovione is recognized as a reliable partner in inhalation product development. We are the only independent company with expertise in every aspect of inhalation, from chemical development to particle design, from device to formulation development."

"We will now be able to accelerate both the program with Sankyo and marketing this potentially important new product to other licensees," added Peter Cook, Biota's CEO. "Biota has an impressive pipeline in anti-viral drugs, and we expect that inhaled LANIs will offer further effective and convenient first line of defense against the influenza virus."

Hovione is a specialist company in Active Pharmaceutical Ingredient (API) manufacturing and inhaled formulation development. Through its expertise in API processing, Hovione has acquired significant know-how in particle design and engineering. This knowledge has permitted Hovione to offer a unique range of compliant services in API process development, particle design, and inhalation formulations. Development services are available through Hovione facilities in Loures, Portugal, and in New Jersey.

Daiichi Sankyo Company, Limited was established in 2005 as the joint holding company of two major Japanese pharmaceutical companies (Sankyo Co., Ltd., and Daiichi Pharmaceutical Co., Ltd.). Daiichi Sankyo is a global pharmaceutical innovator, continuously generating innovative drugs and services and maximizing its corporate value.

Based in Melbourne, Australia, Biota has a proud history as a world-leader in antiviral drug development and a track-record of bringing products to the market. Biota's initial success was the discovery of zanamivir, the first-in-class neuraminidase inhibitor for the treatment and prevention of influenza. Zanamivir is licensed to GlaxoSmithKline and marketed as Relenza, which is used to treat seasonal influenza and is currently being stockpiled by various governments for defense against possible pandemic outbreaks of avian (bird) influenza. The company also developed influenza diagnostics FLU OIA and FLU OIA A/B, currently marketed by Inverness Medical as part of the BioStar range.

Market News and Trends

SCOLR Pharma Announces Research Collaboration With BioCryst Pharmaceuticals

SCOLR Pharma, Inc. recently announced it is collaborating with BioCryst Pharmaceuticals to develop an oral formulation of peramivir using SCOLR's proprietary CDT® drug delivery platform. SCOLR Pharma had previously announced a research collaboration with an undisclosed US based biopharmaceutical company on September 21, 2006.

Peramivir is a novel therapeutic being developed by BioCryst for treatment of seasonal and life-threatening influenza with a focus on intravenous and intramuscular delivery. The goal of the collaboration is to develop an oral delivery system for peramivir that improves bioavailability. BioCryst will share all appropriate peramivir preclinical and clinical data with SCOLR to support its development efforts. If successful, the parties expect to enter a license agreement that would provide for the potential commercialization of peramivir.

BioCryst was recently awarded a $102.6 million, 4-year contract from the US Department of Health and Human Services (DHHS) to develop the influenza neuraminidase inhibitor, peramivir, for the treatment of seasonal and life-threatening influenza, including avian flu. BioCryst announced this past January that it had initiated a Phase II clinical trial of an intramuscular formulation of the drug peramivir.

Daniel O. Wilds, President and CEO of SCOLR Pharma, Inc., said, "We are very excited about the opportunity to work together with BioCryst in the development of an oral formulation of peramivir, which if successful, could provide patients with an important new option in the treatment of seasonal as well as life-threatening flu."

Peramivir is part of a new class of antiviral agents that inhibit influenza viral neuraminidase, an enzyme essential for the influenza virus to spread and infect its hosts. The drug was designed to treat and prevent various types of flu, and in laboratory tests has been shown to be a potent and selective inhibitor of influenza A and B neuraminidases. Additionally, in preclinical studies, peramivir has shown encouraging activity against H5N1 avian influenza, leading researchers to believe that in the proper formulation, the drug may be effective against that virus, as well as against other life-threatening influenza strains that infect humans.

BioCryst Pharmaceuticals, Inc. is a leader in the use of crystallography and structure-based drug design for the development of novel therapeutics to treat cancer, cardiovascular diseases, autoimmune diseases, and viral infections. The company is advancing multiple internal programs toward potential commercialization, including Fodosine in oncology, BCX-4208 in transplantation and autoimmune diseases, peramivir in seasonal and life-threatening influenza, and BCX-4678 in hepatitis C.

Based in Bellevue, Washington, SCOLR Pharma, Inc. is a specialty pharmaceutical company leveraging formulation expertise and its patented CDT platform to introduce distinctive and novel OTC products, prescription drugs, and dietary supplements. SCOLR Pharma's CDT drug delivery platform provides distinctive products with tangible benefits for the consumer and competitive commercial advantages for licensees.

Accentia Biopharmaceuticals Acquires Worldwide Exclusive License to Revimmune for All Autoimmune Diseases

Accentia Biopharmaceuticals, Inc. has recently acquired the exclusive worldwide rights for Revimmune™, a patent-pending pharmaceutical treatment in late-stage development for a variety of autoimmune diseases. The in-license advances the company's strategy of acquiring late-stage drug candidates that can benefit from the 505(b)(2) regulatory pathway.

Revimmune uses an ultra-high intensity, short-course of an intravenous formulation of an approved drug (cyclophosphamide), in a new patent-pending method to "reboot" a patient's immune system, thereby eliminating the autoimmunity, whereas current therapies, including oral cyclophosphamide, are used chronically to try to suppress the inflammation of autoimmunity. Based on long-term follow-up showing complete remissions, there is substantial evidence that Revimmune has the potential to cure cases of severe refractory autoimmune diseases, such as aplastic anemia and myasthenia gravis. Accentia's lead indication for Revimmune is multiple sclerosis (MS).

"Based on follow-up of up to 2 years, most people have a substantial improvement, and many have a complete elimination of disease activity," said Dr. Douglas Kerr, Associate Professor of Neurology and the Principal Investigator for the ongoing MS study with Revimmune at Johns Hopkins University School of Medicine. The Co-principal Investigators on this study are Drs. Daniel Drachman and Robert Brodsky.

The Revimmune license covers all of the estimated 80 autoimmune diseases that are currently recognized. These include multiple sclerosis, systemic lupus, juvenile diabetes mellitus, rheumatoid arthritis, Crohn's disease, myasthenia gravis, and scleroderma. To date, over 175 patients, mostly those with severe refractory autoimmune diseases, have been treated with Revimmune. The company believes that Revimmune is a "platform" technology that can be used in any autoimmune disease. Revimmune can be administered as an inpatient or outpatient infusion for 4 hours per day for 4 consecutive days. Patients can recover at home while their immune system reconstitutes itself over a 2- to 3-week period. Revimmune includes a risk management program to enhance patient safety by ensuring appropriate patient selection, supportive care, and tracking of outcomes data.

Developed by Dr. Richard Jones, Dr. Robert Brodsky, and colleagues at the Johns Hopkins University School of Medicine, Revimmune works by temporarily eliminating peripheral immune cells, including the immune cells causing the autoimmunity, while selectively sparing the stem cells in the bone marrow. Investigators at Hopkins discovered that stem cells uniquely have high levels of a particular protective enzyme that can be measured in advance of therapy, which makes them impervious to Revimmune, and allows the surviving stem cells to give rise to the new immune system over 2 to 3 weeks. The newly reconstituted peripheral immune system typically lacks the misdirected immunity to self-antigens, which is characteristic of autoimmune diseases.

"Revimmune complements our strategy of developing late-stage, "disruptive" clinical products based on already approved active pharmaceutical ingredients. This product strategy is the basis of our lead product, SinuNase™, in which the active pharmaceutical ingredient is the approved antifungal, amphotericin B, and which we were able to advance directly into a Fast-Tracked Phase III clinical trial for chronic sinusitis," said Dr. Frank E. O'Donnell, Jr., Chairman and Chief Executive Officer of Accentia Biopharmaceuticals. "Revimmune offers the hope of sustained remissions and cures for autoimmune diseases, such as MS, thereby eliminating or reducing dependence on chronic immunosuppressive therapies, which we believe are more toxic, carcinogenic, inadequate, inconvenient, and very expensive, especially in the case of monoclonal antibodies. Revimmune's use would also obviate the risk and expense of allogeneic (donor) stem cell transplantation to treat severe cases of autoimmune diseases. After consultation with the FDA, Accentia is preparing an IND for severe refractory multiple sclerosis and is proposing to enter Phase III clinical trials to support licensure under the 505(b)(2) regulatory pathway. The IND incorporates a novel risk management program to ensure appropriate patient selection, supportive care, and tracking of outcomes, which we believe will be critical to reimbursement coverage and malpractice protection for healthcare providers."

The technology is being licensed from Revimmune, LLC, a Hopkins Capital Group II LLC (HCG II) portfolio company, which holds the exclusive license for the technology from the Johns Hopkins University. HCG II had been exploring a license to the technology since 2003. Dr. Frank E. O'Donnell Jr. is a Managing Partner of HCG II.

Topigen & Novagali Enter Strategic Collaboration for Allergic Ocular Diseases & Allergic Rhinitis

Topigen Pharmaceuticals Inc., a development-stage biopharmaceutical company specializing in respiratory disorders, and Novagali Pharma S.A., a specialty biopharmaceutical company developing novel ophthalmic products, recently announced the initiation of a strategic collaboration and cross-license agreement.

Under the terms of the agreement, Novagali will receive an exclusive worldwide license to develop and commercialize an ophthalmic product based on Topigen's multi-targeted, RNA-targeting platform technology for the treatment and prevention of allergic eye diseases. Topigen will receive an exclusive license to Novagali's Novasorb topical delivery technology for use in formulating and developing an RNA-targeted therapy for treating respiratory conditions, such as allergic rhinitis.

Topigen and Novagali will collaborate to develop ocular and nasal forms of RNA-targeting product candidates based on Novagali's Novasorb topical delivery technology. Topigen and Novagali will develop formulations designed to improve the bioadhesion and hence the efficacy of RNA-targeting therapeutics delivered to the nasal membrane and ocular surface. The Novasorb technology is a delivery system that provides significantly improved retention time for therapeutic compounds in tissues, such as the cornea and conjunctiva and other membrane surfaces, including those within the nose.

The terms in the agreement enable Novagali to develop its own ophthalmic product based on Topigen's multi-targeted, RNA-targeting platform technology for the treatment and prevention of allergic eye diseases, and for Topigen to develop its own RNA-targeting products for allergic rhinitis based on the formulations developed using the Novasorb technology. Financial terms of the agreement were not disclosed.

Jerome Martinez, President and Chief Executive Officer of Novagali Pharma, commented, "We think it is a perfect fit to collaborate with Topigen, for the development of therapeutics for allergic eye diseases. In its respiratory development programs, Topigen has successfully validated its multi-targeted RNA approach in initial Phase II studies in patients with asthma. The types of chemokines and cytokines that have been shown to be important mediators in asthma are also mediators in allergic inflammatory conditions affecting the eye. Combined with our Novasorb topical delivery technology, we believe we can develop a better alternative to current therapies for the treatment and prevention of allergic eye diseases. This project would strengthen our pipeline position in the area of ocular allergic disease, an expanding market that exceeded $1 billion, worldwide last year."

"We are excited to be able to apply our multi-targeted, RNA-targeting technology for the first time in ophthalmic indications," added Paul K. Wotton, PhD, President and Chief Executive Officer of Topigen. "Novagali brings significant expertise in ocular disease treatment and drug delivery. This collaboration will help us to expand into other therapeutic areas, and we will also reap the benefit of applying Novagali's Novasorb topical delivery technology to develop one of our lead products for allergic rhinitis. This significantly expands the application of our platform technology and broadens our product portfolio."

Novasorb is a cationic emulsion delivery system that provides significantly improved drug spreading and binding to tissues, such as the cornea and conjunctiva. Studies have shown that Novasorb significantly improves absorption and/or efficacy of drugs in eye tissues. The technology can also easily be used for nasal delivery with the same benefits.

RNA-targeting oligonucleotides are chemically-modified molecules (nucleotides) that are designed to bind to a specific sequence of a messenger RNA's (mRNA) target through base-pairing interactions, thereby interfering with expression of the protein encoded by the mRNA. Scientists are using RNA-targeting oligonucleotides to design new, more effective drugs to inhibit gene expression and production of abnormal levels of cell proteins involved in diseases.

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Market News and Trends

Cannasat Therapeutics & IntelGenx Enter to Develop Cannabinoid-Based Products for Mood Disorders

Cannasat Therapeutics Inc. and IntelGenx Corp. recently announced a long-term collaborative agreement to co-develop a novel cannabinoid-based product, CAT 320, through a combination of Cannasat's and IntelGenx's proprietary drug delivery technologies.

Cannasat is enthusiastic about CAT 320, a product that targets the endocannabinoid system to treat mood disorders, such as anxiety and depression. Mood disorders have been estimated to affect 9% to 20% of the population, and an estimated 18% of North American adults yearly suffer from an anxiety disorder. These disorders are currently treated with drugs that have estimated annual worldwide sales of $20 billion.

Anxiety disorders are considered the most prevalent of psychiatric disorders. Anxiety is an unpleasant, emotional state that is hard to control and that often interferes with daily functioning. It involves a complex combination of emotions that include fear, apprehension, and worry. Poor diagnosis rates and treatment outcomes mean there is still considerable opportunity for Cannasat to move into the anxiety and/or depression markets. Cannasat will leverage IntelGenx's significant experience in developing unique oral, sublingual, and transdermal formulations. IntelGenx's expertise will help address the challenges of achieving rapid onset, improving therapeutic efficacy, and minimizing the total dose required to treat disease conditions.

"We are excited to work with IntelGenx to develop a new cannabinoid pharmaceutical product that could be used to treat indications, such as anxiety where there is currently a large unmet medical need for new therapies. IntelGenx's technology platform complements our existing drug delivery technologies and provides us an opportunity to broaden our growing intellectual property portfolio and product development pipeline." said David Hill, CEO of Cannasat Therapeutics.

"The partnership with Cannasat represents an important element in the development of our company, and we are excited to expand our strategic alliance with Cannasat to include the development of new cannabinoid-based pharmaceuticals that could potentially address a wide range of therapeutic indications," added Dr. Horst Zerbe, CEO of IntelGenx Corp.

IntelGenx Corp. is a drug delivery company focused on the development of oral controlled-release products as well as novel rapidly disintegrating delivery systems. The company uses its unique multiple-layer delivery system to provide zero-order release of active drugs in the gastro-intestinal tract. IntelGenx has also developed novel delivery technologies for the rapid delivery of pharmaceutically active substances in the oral cavity based on its experience with rapidly disintegrating films. The company's research and development pipeline includes products for the treatment of osteoarthritis, pain management, smoking cessation, and depression.

Cannasat Therapeutics is researching the therapeutic benefits of cannabis and developing novel cannabinoid pharmaceutical products. Cannasat is pursuing two complementary business strategies. The first consists of development of novel cannabinoid-based pharmaceutical products through application of drug delivery technologies to be introduced to the market through the traditional regulatory drug approval process. The second is to promote medicinal cannabis research and education with Cannasat's business partner, Prairie Plant Systems Inc., the sole government licensed grower and distributor of medicinal cannabis in Canada.

Abeille Pharmaceuticals Licenses AB-1001 to SymBio Pharmaceuticals for Commercialization in Japan & Pacific Rim Countries

Abeille Pharmaceuticals, Inc., and SymBio Pharmaceuticals Limited recently announced the signing of an exclusive license and distribution agreement to develop and sell AB-1001, Abeille's transdermal patch for emesis, in Japan, China (including Hong Kong), Korea, Taiwan, and Singapore. For the right to develop and sell AB-1001 in the aforementioned territories, SymBio will pay Abeille an up-front licensing fee, and payments based on achievement of specific milestones, that could total up to $21 million. The agreement also calls for double-digit royalty payments on commercial sales. As part of the agreement, Abeille has also granted to SymBio the right of first refusal on Abeille's next product in the field.

AB-1001, is a transdermal patch for chemotherapy-induced nausea and vomiting (CINV). AB-1001 is designed to deliver a commercially available 5HT3-antagonist through the skin for a continuous period of up to 5 days, thereby providing the patient with sustained relief for CINV. Abeille has successfully completed a Phase I pharmacokinetic study and a Phase II irritation and sensitization study under a US IND. In late 2006, the company reached an agreement through a Special Protocol Assessment (SPA) with the FDA on its intended Phase III study design and intends to initiate a multinational Phase III trial in 2Q 2007.

"We are extremely pleased with the signing of this license and distribution agreement with SymBio." said Suresh Borsadia, President and CEO of Abeille. "In SymBio, we have a partner that shares our vision of bringing quality products to patients in need with speed to market. Mr. Fuminori Yoshida, President and CEO of SymBio, has assembled an experienced team of senior executives at SymBio who have a track-record of developing and marketing oncology-related products in Japan and the region. This partnership leverages that experience to ensure that the product is developed to maximize commercial success."

"We are impressed with Abeille's expertise in product development of innovative drug delivery systems, and we are looking forward to our collaboration with them," added Fuminori Yoshida, President and CEO of SymBio. "This collaboration for the development of the transdermal patch for chemotherapy-induced nausea and vomiting as well as the next product will be complementary to our pipeline portfolio that is focused on therapeutics in oncology and hematology. I am very excited to partner with Abeille to deliver important supportive care products to cancer patients in Japan, China, Korea, Taiwan, and Singapore."

Abeille Pharmaceuticals, Inc. is a privately held pharmaceutical company based in Princeton, New Jersey. The company is focused on the formulation of products by applying advanced delivery technologies to existing drugs. These advanced delivery technologies include oral controlled-release and transdermal delivery systems. The new products may benefit patients by requiring a lower dose of medicine, reduced side effects, and easier administration of medication, thereby encouraging a patient to use the medication as prescribed. Abeille is dedicated to the development and commercialization of products that address unmet medical needs and improve the quality of life for patients. The company's initial focus will be on drugs used to treat oncology-related discomforts, diabetes and metabolic disorders, and CNS.

SymBio Pharmaceuticals' focus is on oncology/hematology and autoimmune disease therapies. Established in 2005 by Fuminori Yoshida, who previously served as both Corporate Vice President of Amgen Inc. and President of Amgen Japan, SymBio Pharmaceuticals' underlying corporate philosophy is delivering hope to patients in need, and the company aims to address unmet medical needs of patients in Japan by cultivating a mutually beneficial or symbiotic relationship among physicians, scientists, regulatory agencies, and investors. SymBio Pharmaceuticals core philosophy is that profitability and socially responsibility as a pharmaceutical enterprise can go hand in hand, and need not be mutually exclusive.

Market News and Trends

Acrux & Organon to Develop Contraceptive Sprays

Acrux, a drug delivery company, recently announced it has signed an agreement with Organon, the human healthcare business unit of Akzo Nobel. Organon and Acrux will develop and commercialize contraceptives delivered through the skin using Acrux's unique spray technology.

"We are delighted and proud that Organon, with its renowned experience and expertise in contraception, has recognized the benefits that our innovative technology can provide," said Acrux CEO Richard Treagus. "We are looking forward to working closely with Organon to realize the commercial potential in this large market."

Organon's executive Vice President, Research and Development, David Nicholson, added, "Organon recognizes the importance of contraceptive choice and offers one of the most comprehensive portfolios of effective, innovative, and appealing methods available. This collaboration with Acrux is part of our strategy to vigorously pursue alternative options to extend choices even further."

Under the agreement, Organon has licensed Acrux's technology for use with selected contraceptive compounds. Acrux will be responsible for developing formulations of such contraceptive compounds and upon successful completion of this program, Organon will undertake and fund all clinical trials, regulatory submissions, manufacturing, and marketing.

For each contraceptive compound that Organon selects to develop, Acrux may receive payments totaling between $12 million and $16 million as development and regulatory milestones are achieved. Acrux will also earn royalties on worldwide sales of each product.

Acrux is free to develop and commercialize sprays containing other contraceptive compounds, including Nestorone, which it is currently advancing through clinical trials.

Worldwide sales of hormonal contraceptive products in 2006 were approximately $6.7 billion. The availability of a broad range of effective, safe, and appealing contraceptive products is viewed as one of the most important issues in contraception. This enables women to choose the method most appropriate to their needs and lifestyle.

Acrux is an Australian drug delivery company developing and commercializing a range of patient-preferred, patented pharmaceutical products for global markets, using its innovative technology to administer drugs through the skin. Fast-drying, invisible sprays or liquids provide a delivery platform with low or no skin irritation; superior cosmetic acceptability; and simple, accurate, and flexible dosing. The technology platform is covered by broad and well-differentiated issued patents. Acrux's products in clinical development include Estradiol MDTS (EvaMist in the US) to treat menopause symptoms; Testosterone MDTS to treat decreased libido in women; Nestorone MDTS contraceptive spray for women; Fentanyl UDTS to treat chronic pain; and Testosterone MD-Lotion to treat testosterone deficiency in men.

Acrux has licensed worldwide rights for certain MDTS contraceptives to Organon, USA rights for Estradiol MDTS and Testosterone MDTS to VIVUS, and AUS/NZ distribution rights for Testosterone MDTS and Fentanyl UDTS to CSL Limited. Acrux has also licensed its technology to Eli Lilly and Company for veterinary healthcare products.

Organon creates, manufactures, and markets innovative prescription medicines that improve the health and quality of human life. Through a combination of innovation and business partnerships, Organon seeks to leverage its position as a leading biopharmaceutical company in each of its core therapeutic fields: fertility, gynecology, and selected areas of anesthesia. It has extensive expertise in neuroscience and a rich and focused R&D program. Research areas also include immunology and specific areas of oncology.

Market News and Trends

PPD, Inc. Licenses Statin From Ranbaxy Laboratories

Ranbaxy Laboratories Ltd., India, and PPD, Inc. recently announced that PPD has acquired an exclusive worldwide license to develop, manufacture, and market Ranbaxy's novel statin for the treatment of dyslipidemia.

The preclinical toxicology, drug metabolism, and pharmacokinetic data suggest that the Ranbaxy statin has the potential to offer an improved safety profile over currently marketed statins. PPD plans to conduct additional preclinical studies and file an investigational new drug application with the US Food and Drug Administration in April 2007.

Under the terms of the agreement, Ranbaxy will be entitled to receive milestone payments upon the occurrence of specified clinical events. In the event of approval to market a drug product, Ranbaxy will be entitled to receive royalties on sales of the drug and sales-based milestones. PPD will be responsible for all costs and expenses associated with the development and commercialization of the compound, including preclinical and clinical studies. Ranbaxy has retained co-marketing rights to the compound in India.

"This is yet another milestone in Ranbaxy's evolution as a strong global research company," said Malvinder Singh, Chief Executive Officer and Managing Director of Ranbaxy. "We are pleased to partner with PPD in taking this potential drug forward, promising superior treatment for dyslipidemia and related areas."

In announcing the agreement, Fred Eshelman, Chief Executive Officer of PPD, said, "The opportunity to develop and commercialize Ranbaxy's statin is a logical extension of our compound partnering program. It meets the rigorous requirements for our partnering strategy and further strengthens our metabolic franchise. We look forward to deploying our development expertise and resources to move this compound ahead."

Commenting on the success, Pradip Bhatnagar, Vice President, New Drug Discovery Research at Ranbaxy, said, "This is the second compound from Ranbaxy's New Drug Discovery Research, and we are glad to have achieved this milestone."

According to the American Heart Association, statins are the most widely prescribed class of drugs for lowering cholesterol. A recent series of trials using statins demonstrated conclusively that lowering total cholesterol and LDL-cholesterol reduces the chance of having a heart attack, needing bypass surgery or angioplasty, and dying of coronary heart disease-related causes. Worldwide, cholesterol lowering drugs accounted for $32.4 billion in sales for 2005, according to IMS Health.

PPD also announced it is not changing its previously issued 2007 financial guidance as a result of this transaction.

Ranbaxy Laboratories Ltd., headquartered in India, is an integrated, research-based, international pharmaceutical company producing a wide range of quality, affordable generic medicines, trusted by healthcare professionals and patients across geographies. Ranbaxy's continued focus on R&D has resulted in several approvals in developed markets and significant progress in New Drug Discovery Research. The company's foray into Novel Drug Delivery Systems has led to proprietary platform technologies, resulting in a number of products under development.

PPD is a leading global contract research organization providing discovery, development, and post-approval services as well as compound partnering programs. Its clients and partners include pharmaceutical, biotechnology, medical device, academic, and government organizations. With offices in 28 countries and more than 9,100 professionals worldwide, PPD applies innovative technologies, therapeutic expertise, and a commitment to quality to help its clients and partners maximize returns on their R&D investments and accelerate the delivery of safe and effective therapeutics to patients.

MonoSolRx Enters License & Collaboration Agreement With Adams Respiratory Therapeutics

MonoSolRx, LLC, a leading pharmaceutical oral thin film company, recently announced that it had entered into a license and collaboration agreement with Adams Respiratory Therapeutics, Inc. MonoSolRx will use its rapid dissolve oral thin film drug delivery platform to develop prescription and over-the-counter (OTC) products for Adams.

"This agreement, with a market innovator and leader like Adams, validates the strength of our technology, development capabilities, manufacturing capacity, and approach to partnering," said President and Chief Executive A. Mark Schobel. "Oral thin film has broad application in the prescription pharmaceutical market. We are very excited about the partnership with Adams."

Adams Chief Operating Officer, Robert D. Casale, said, "Currently, there are no prescription respiratory products that employ this unique thin film delivery technology, and we believe there are several product targets that would benefit from the application of this technology."

Under the terms of the agreement, MonoSolRx provides an exclusive, royalty bearing, non-transferable license to use its proprietary thin film drug delivery technology to develop and market two or more respiratory products in North America. The initial prescription product has been identified but not yet disclosed. Adams also has the right of first refusal to develop a limited number of additional high-value prescription candidates in the respiratory space. Under a separate product supply agreement, MonoSolRx has agreed to manufacture and supply finished products that result from the collaboration.

MonoSolRx is responsible for completing the product development work and will be eligible to receive payments for completing certain predefined development milestones. Adams will be responsible for performing all aspects of clinical development and regulatory submission as well as marketing and distribution. Financial terms of the agreement are not being disclosed.

MonoSolRx is a thin film drug delivery company specializing in proprietary dissolving thin film products. Its thin film drug delivery dosage form is similar in size, shape, and thickness to a postage stamp and dissolves readily on the tongue for easy use by patients. Its thin film drug delivery technology is now used in the OTC marketplace and is currently emerging in the prescription drug market.

Adams is a specialty pharmaceutical company focused on the late-stage development, commercialization, and marketing of OTC and prescription pharmaceuticals for the treatment of respiratory disorders.

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COMBINATION UPDATE

Successful Convergence Strategies

By: Christine M. Ford

The benefits of merging pharmaceuticals, biological products, and medical devices into combination products, such as inhaled insulin, coated artificial joints, drug-eluting cardiovascular stents, and surgical kits, are well known. Combination products can improve the safety, precision, and efficacy of clinical therapies or make treatment simpler and more convenient to healthcare providers and patients.

But combination product development involves unique challenges. To succeed in this marketplace, pharmaceutical, biotech, and medical device firms need to develop convergence strategies for working with partners and across disciplines.

A successful convergence strategy will be grounded in a company's core business. For device makers, combination products may present new opportunities to implement their proven technologies. Pharmaceutical or biotechnology companies may be able to use combination products to market their drugs or biologics in new ways — in some cases extending their patent life cycles. By building on what they already do well, companies can utilize existing distribution channels and sales teams to decrease entry costs and mitigate risks.

Firms also need to have a clear idea of the value gained from combining previously distinct products or technologies. Are there new treatments or therapeutic trends that set the stage for combination products? It's important to consult with end users through physician advisory boards, medical societies, and market research to pinpoint areas ripe for innovation. It can also be useful to develop strategies to work around any potential barriers to adoption. For example, will a new product require significant changes in practice workflow, or new payment codes from the Centers for Medicare and Medicaid Services?

Large organizations may have the internal resources needed to develop and manufacture combination products, but most companies will have to pursue partnerships, in-licensing or out-licensing arrangements, or acquisitions. Joint ventures should be approached as opportunities to seek out partners that have the complementary skills and assets needed to bring an innovative concept to fruition. Biotech or drug companies may enlist device company partners to develop a particular delivery system; device companies may actively seek out biotech or pharmaceutical collaborators. It may be useful to outsource some aspects of the process, from research and development through to equipment design and testing. This can potentially speed time to market and lower costs.

Whether pursuing joint ventures or outsourcing, it's important for manufacturers to protect their intellectual property. Even if they are not ready or able to pursue patent protection, firms should document the expertise behind their technologies or processes, taking into account their current and potential end-use applications. This kind of "defensive" publishing strategy can build evidence that a company owns a particular area of intellectual property in a combination product. Doing so will provide leverage in partnership arrangements, and make the case for appropriate credit in any eventual disputes.

It's also important that all parties collaborate. Engineers, scientists, and product managers will have to work across disciplines and reach out to technical, legal, business, and marketing personnel to discuss a product's feasibility and develop a commercialization strategy. Notably, this might entail product and process characterization and testing earlier than is typical in the development cycle.

To avoid surprises, manufacturers should discuss their plans with the FDA at the earliest possible stage. Drugs, devices, and biological products each have their own regulatory pathways, with the FDA's Office of Combination Products (OCP) assigning products to the appropriate regulatory center based on their "primary mode of action." The OCP website (www.fda.gov/oc/combination/) includes guidance for combination product applicants, including explanations of the necessary scientific and technical information. It also includes examples of recently approved combination products to provide a sense of the review process thus far. Manufacturers should request pre-submission meetings to seek advice on the best approach for clinical testing and evaluation of their product.

It's clear that combination products are changing the landscape of the healthcare industry, enabling companies to enter new market segments or diversify their product portfolios. Yet, the complexity of such products entails design, production, and approval challenges, making it crucial for manufacturers to develop a convergence strategy. Even if firms are not yet ready to enter this field, they should begin to explore the tools and partners they will need to succeed in it. ◆

BIOGRAPHY

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

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Product-By-Process Claims: Different Interpretations in Different Settings?

By: Clifford M. Davidson, Esq. & Benjamin S. DiMarco, Esq.

What aspects of a new product can be patent protected? Of course, the active pharmaceutical ingredient (API) is often a key focus of "composition-of-matter" patent claims. Further protection is often available for the combination of the API with key pharmaceutical excipients (the "drug product"). Sometimes, there is an opportunity to seek patent protection for a novel therapeutic treatment using the drug/drug product ("method of treatment" claims). All of the aforementioned types of patent claims are particularly useful because they result in patents that can be listed in the FDA's *Orange Book*.

There are other types of patent claims that are not listable in the *Orange Book* that are nonetheless valuable. Such types of claims include method of manufacture, intermediates, etc.

Hybrid "product-by-process" claims, which are the focus of this article, are listable in the *Orange Book* when the product is novel. But what do product-by-process claims actually cover? There has been quite a bit of confusion not only in the industry, but also in the courts as to whether product-by-process claims cover the product, the process, or both. As the reader will ascertain from the decisions of the courts, the patent coverage afforded by product-by-process claims has been a moving target.

BACKGROUND OF PRODUCT-BY-PROCESS CLAIMS

The Supreme Court has described the product-by-process claim as "one in which the product is defined at least in part in terms of the method or process by which it is made" [Bonito Boats, Inc. v. Thunder Craft Boats, Inc., 489 U.S. 141, 158 (U.S. 1989)]. Initially, product-by-process claims were drafted out of necessity as a way to claim a product that resists definition by other than the process by which it is made [Thorpe, 777 F.2d 695, 697 (Fed. Cir. 1985)]. The original product-by-process claim allowed the inventor to say "the invention is directed to a product that is made from the following manufacturing procedure." Such claims do not necessarily provide a description of the product, only the procedure for making it. One could envision a situation in which the technology (eg, in the biotechnology field) has not fully developed to the level where the product could be sufficiently described to satisfy the written description requirement of 35 U.S.C. § 112 ¶ 1. In this case, the original product-by-process claim would be appropriate.

Eventually, the courts embraced product-by-process claims even where the structure of the product could be adequately described. For example, in 1969, the predecessor court to the Federal Circuit (ie, the Court of Customs and Patent Appeals), reversed a lower court decision finding that a product-by-process claim was improper because the applicant could have claimed the invention without relying on the process [Pilkington, 56 C.C.P.A. 1237, 411 F.2d 1345 (C.C.P.A. 1969)].

The Federal Circuit has struggled to determine whether product-by-process claims are limited by the recited process steps. In the 1991 Scripps decision, one panel of Judges on the Federal Circuit held that process steps are not limiting under an infringement analysis (and therefore claims cover the product without limitation to the delineated process for making it). In 1992, another panel of Judges on the Federal Circuit in its Atlantic decision side-stepped the Scripps decision, ruling that process steps are limiting. To add to the confusion, in the recent (2006) SmithKline decision, the Federal Circuit ruled that for purposes of validity, process limitations do

not limit the claimed product. Each of these cases will be discussed further.

EARLY TREATMENT OF PRODUCT-BY-PROCESS CLAIM SCOPE IN SCRIPPS CLINIC

In Scripps Clinic & Research Foundation v. Genentech, Inc., 927 F.2d 1565 (Fed. Cir. 1991), the product-by-process claims were directed to a highly purified and concentrated human or porcine clotting factor VIII:C prepared in accordance with the method recited in the first claim of the patent. The first claim was directed to an improved method of preparing Factor VIII procoagulant activity protein comprising the steps of (a) adsorbing a VIII:C/VIII:RP complex from a plasma or commercial concentrate source onto particles bound to a monoclonal antibody specific to VIII:RP, (b) eluting the VIII:C, (c) adsorbing the VIII:C obtained in step (b) in another adsorption to concentrate and further purify the same, (d) eluting the adsorbed VIII:C, and (e) recovering highly purified and concentrated VIII:C. Here, utilizing the product-by-process claim appears to be out of necessity where the product is new and could only be described by the process of manufacture.

Scripps Clinic asserted that the disputed product-by-process claims were infringed by Genetech's highly purified recombinantly produced Factor VIII:C. The lower court denied Scripps Clinic summary judgment of infringement. On appeal, the Federal Circuit considered whether the recited process in a product-by-process claim was limiting with respect to the patentability of such a claim, and whether the claim was infringed. The Court began by holding that for purposes of patentability, a product is not limited by the recited process in a product-by-process claim. The court then stated that claims should be construed the same way for validity and for infringement. The Federal Circuit concluded that for determining patentability and for determining whether a product infringes, product-by-process claims are not limited by the recited process steps [Scripps Clinic, 927 F.2d at 1583]. Therefore, the Court concluded that the asserted claims were infringed by the Genetech product.

SUBSEQUENT TREATMENT OF PRODUCT-BY-PROCESS CLAIMS SCOPE IN ATLANTIC

The following year, the Federal Circuit decided another case involving a product-by-process claim [Atlantic Thermoplastics Co. v. Faytex Corp., 970 F.2d 834 (Fed. Cir. 1992)]. In Atlantic, the disputed product-by-process claim was directed to a shoe innersole made from a process including introducing an expandable polyurethane material [in a liquid state], into a mold and inserting an elastomeric heel portion [in a solid state], into the mold. In contrast to the product in Scripps, the Atlantic product could have adequately been described without reference to the process of manufacture.

Atlantic asserted that the products sold by Faytex, although made by a different process, were indistinguishable from the product-by-process claim in question. The Faytex innersoles were made by a process that involved injecting (ie, pouring) into a mold, a liquid polyurethane material, and a liquid elastomeric heel material. The district court limited the product in the product-by-process claim to exclude any product that involved pouring the heel portion material into the mold. Therefore, because the Faytex product involved pouring the elastomeric heel portion into the mold, the district court held that it did not infringe the asserted claim.

The Atlantic court's decision, holding that process steps in an infringement setting are limiting, was in direct contrast to the earlier Scripps decision. The Atlantic court justified its decision to not follow Scripps in footnote two of this case, stating that *"a decision that fails to consider Supreme [C]ourt precedent does not control if the court determines that the prior panel would have reached a different conclusion if it had considered controlling precedent."* The Atlantic court cited to several United States Supreme Court cases concerning product claims reciting process steps, such as Cochrane v. Badische Anilin & Soda Fabrik, 111 U.S. 293 (U.S. 1884) and General Electric Co. v. Wabash Appliance Corp., 304 U.S. 364 (U.S. 1938), both holding that process steps did limit the claimed product in an infringement setting. The Atlantic court reasoned that the Scripps court did not control because the Scripps panel would have come to a

different conclusion if it considered these earlier Supreme Court cases.

The Atlantic court further held that claims are construed differently for purposes of patentability at the Patent and Trademark Office and for validity and infringement in the courts. According to the Atlantic court, for the purpose of patentability analysis, a product-by-process claim is based on the product itself, and not the delineated process of manufacture: if the product (without limitation to any particular process of manufacture) is not novel, the claim should not be allowed [Atlantic Thermoplastics Co., 970 F.2d at 846; citing In re Zletz, 893 F.2d 319, 321 (Fed. Cir. 1989)]. In contrast, the Atlantic court considered the delineated process steps to be limitations that must be considered during subsequent litigation for the purpose of considering issues of invalidity or infringement. The Atlantic court held in two successive paragraphs that (1) *"claims mean the same for infringement and validity"* and (2) *"an accused infringer can avoid infringement by showing that the accused device lacks even a single claim limitation . . . [t]hus ignoring the claim limitations of a product-by-process claim would clash directly with basic patent principles enunciated by the Supreme Court and this court."* [Atlantic Thermoplastics Co., 970 F.2d at 846]. The Atlantic court believed that litigants are capable of investing the resources necessary to provide the data showing whether it is the product or only the process of making the product that is novel. Although it now rendered two conflicting decisions in as many years, the Federal Circuit refused to "legitimize" its holding in Atlantic by conducting a rehearing of the case *en banc*.[1]

RECENT TREATMENT OF PRODUCT-BY-PROCESS CLAIMS

The Federal Circuit seems to have contradicted its reasoning in Atlantic, now ignoring process limitations in assessing validity in SmithKline Beecham Corp. v. Apotex Corp., 439 F.3d 1312, (Fed. Cir. 2006). Claims 1 and 2 at issue in SmithKline recite:

1. A pharmaceutical composition in tablet form containing paroxetine, produced on a commercial scale by a process that comprises the steps of:

   a) dry admixing paroxetine and excipients in a mixer to form a mixture; or

   b) dry admixing paroxetine and excipients, compressing the resulting combination into a slug material or roller compacting the resulting combination into a strand material, and milling the prepared material into a free flowing mixture; and

   c) compressing the mixture into tablets.

2. A pharmaceutical composition in tablet form according to claim 1 containing an amount of paroxetine selected from 10 mg, 20 mg, 30 mg, 40 mg, and 50 mg wherein the amount of paroxetine is expressed as the free base, produced on a commercial scale by a process that comprises the steps of:

   a) dry admixing paroxetine and excipients in a mixer to form a mixture; or

   b) dry admixing paroxetine and excipients, compressing the resulting combination into a slug material or roller compacting the resulting combination into a strand material, and milling the prepared material into a free flowing mixture; and

   c) compressing the mixture into tablets using a single punch or rotary tablet machine.

According to SmithKline, its earlier patent (which is prior art to the disputed claims) *"disclosed a pharmaceutical composition in tablet form containing paroxetine."* In holding the claims invalid, the lower court relied on the Federal Circuit's earlier holding in Scripps Clinic, which ignored process limitations in product-by-process claims during infringement and applied that reasoning to its validity analysis. The claims were held invalid as being anticipated by the earlier disclosure of the same product because the SmithKline court did not consider the recited process steps as limitations to the product-by-process claims. The Federal Circuit affirmed the lower court's reasoning.

The holding appears to be in sharp contrast to the Federal Circuit's reasoning in Atlantic (holding that process steps are limiting in infringement and validity settings). The SmithKline court held that process steps do not limit product-by-process claims for a validity analysis, and that *"[w]hile the process set forth in the product-by-process may be new, that novelty can only be captured by obtaining a process claim"* [SmithKline, 439 F.3d at 1319]. However, in footnote seven of this case, the Federal Circuit stops short of saying that process limitations never limit products in product-by-process claims [Id., at 1319].

SO, WHAT TO DO NOW?

Product-by-process claims are unique. Federal Circuit inconsistency in construing these claims creates uncertainty for patent practitioners. One would expect to see more frequent patent challenges including charges of invalidity of product-by-process patent claims based on prior art disclosure of the claimed product regardless of the method of manufacture. Prior to SmithKline, a patentee could rebut this prior art challenge, by limiting the product to the recited process steps. This no longer appears to be the case. A good rule of thumb for inventors to follow is that where the inventive process produces a product having discernable (eg, physical, chemical) differences, in addition to presenting composition claims which include limitations to such differences, it still may be possible to claim the product by virtue of the process of making it. However, if the product has no discernible difference from a prior art product (save for a difference in the manufacture of that product), then obtaining valid product-by-process claims will present an uphill battle. ◆

REFERENCE

1. It is noted that where there are two contradictory Federal Circuit decisions, the earlier decision is controlling. Tate Access Floors, Inc. v. Interface Architectural Res., Inc., 279 F.3d 1357, 1366 (Fed. Cir. 2002) citing Kimberly-Clark Corp. v. Ft. Howard Paper Co., 772 F.2d 860, 863, (Fed. Cir. 1985) and Newell Cos., Inc. v. Kenney Mfg. Co., 864 F.2d 757, 765, (Fed. Cir. 1988).

BIOGRAPHY

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EXCIPIENT UPDATE

Sodium Alginate: Physiological Activity, Usage & Potential Applications

By: Geeta Patel, MPharm; Girish Patel, MPharm; Ritesh Patel, MPharm; Jayavadan Patel, PhD; Praful Bharadia, PhD; Madhabhai Patel, PhD

ABSTRACT

Throughout the past few years, medical and pharmaceutical industries have shown an increased interest in biopolymers in general and for alginate in particular. The reason for increased interest is its usefulness in specific applications as it enhances efficient treatment of esophageal reflux, creates multiquality calcium fibers for dermatology and wound healing, and can be used for high- and low-gel strength dental impression materials. In addition, it is an effective natural disintegrant and tablet binder and offers an attractive alternative for sustained-release systems. It is a natural polysaccharide, offers advantages over synthetic polymers as it forms hydrogels, is non-toxic, biocompatible, biodegradable, less expensive, and freely available. All these advantages make alginate very useful material for targeted drug delivery and biomedical applications, especially for control delivery of drugs and other biologically active compounds.

INTRODUCTION

Sodium alginate is slowly soluble in cold water, forming a viscous, colloidal solution. It is insoluble in alcohol and in hydro-alcoholic solutions in which the alcohol content is greater than 30% by weight.[1,2] Various grades of sodium alginate are available, yielding aqueous solutions of varying viscosity within a range of 20 to 400 centipoises (0.02 to 0.4 Pas) in 1% solution at 20°C. A 1% solution in distilled water has a pH of 7.2. Filtration and autoclaving are the least detrimental means of aseptization of alginate solutions.[3] Biocompatibility and immunogenicity of materials are important factors for successful application in carriers for drug delivery. Chemical composition and the mitogenic contaminants found in alginates are the two main contributors to alginate immunogenicity.[4,5] Alginate, with its carboxyl end groups, is classified as an anionic mucoadhesive polymer, and studies have shown that alginate has the highest mucoadhesive strength. This bioadhesive property of sodium alginate serves as a potential advantage in mucosal drug delivery, such as in the gastrointestinal tract and nasopharynx.[6] Because sodium alginate is hygroscopic, the moisture content at equilibrium depends on the relative humidity. Dry alginate is quite stable when stored in a well-closed container at a temperature of 25°C or less. Alginate solutions are stable between pH 4 to 10. Above pH 10, the viscosity of sodium alginate decreases. Solutions of sodium alginate should not be stored in metal containers.[3,7]

ACTIONS & PHARMACOLOGY[8,9]

Sodium alginate may have hypocholesterolemic and glycemic-regulatory activities. It may also have detoxification activity. Sodium alginate has been found to lower cholesterol in animal studies. It is speculated that this may be due to alginate-stimulated increase of fecal bile acid excretion. Sodium alginate has also been demonstrated to lower glucose levels in diabetic animals. The mechanism of this activity is unknown. Sodium alginate binds tightly to such substances as strontium, cadmium, radium, and barium. It also binds to lead, but not as well. Sodium alginate's binding to these substances reduces their absorption. There is little effect on the pharmacokinetics of sodium alginate in humans. It appears to be resistant to digestion by digestive enzymes and is probably fermented, in part, by colonic bacteria to the short-chain fatty acids acetate, propionate, and butyrate.

USE OF ALGINATES IN THE FOOD INDUSTRY & DIETETICS

In the food industry, alginic acid and sodium alginate are used as thickeners and stabilizers in the production of fruit candy, sweets, soft drinks, and in juice settling. Calcium alginate is a thickener, stabilizer, and jelling agent, while sodium alginate is a thickener and stabilizer. As thickeners, alginates are used in the production of such foodstuffs as ice cream, sauces, flavorings, soups, margarine, milk-shakes, juices, liqueurs, structured meat, milk, and fish products. Alginates are also mixed in dough to retard staling, added to jam to reduce the consumption of gelling agents, and improve the structural and ductile properties of the product.[10,11] Alginates and alginic acid are used in the production of transparent films, which are more elastic than cellophane.[12] It is used as protective covering in the food industry, and toxicological studies have proved that alginates are safe for this application. The US FDA has granted GRAS (generally recognized as safe) status to alginates, and the joint food additive committee of the FAO and WHO experts have concluded that the daily permissible dose of sodium alginate is 0 to 50 mg per 1 kg of human body weight.[13]

CURRENT APPLICATIONS OF ALGINATE

Alginic acid and some of its salts have been used in pharmacology for several decades. Sodium alginate was introduced into the US Pharmacopoeia as early as 1938. Alginic acid was entered in the British Pharmaceutical Codex in 1963. As

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a stabilizer of disperse systems, sodium alginate is used in the production of suspensions and emulsions and as a binding agent in tablets. Alginates are also involved in the production of correcting suspensions, gels, and concentrated emulsions on the basis of fats and oils. In the cosmetic industry, sodium alginate is used to thicken and stabilize ointments, creams, face packs, detergents, and hair gels and fixatives.[14]

Wound Healing

The most accessible way in which sodium alginate may be used is to apply it as a powder either pure or mixed with other drugs on septic wounds. The antimicrobial and enzymatic components of the mixture promote elimination of necrotic tissues and microbial bodies, while the polysaccharide base stimulates reparative processes and prepares the wound for scarring. Antimicrobial, adsorptive, and wound-healing effects characterize Algipore, a lyophilized gel containing sodium alginate, calcium gluconate, and Furacillin.[15]

Stomatology

Calcium alginate is used as an absorbing haemostatic agent. When applied to the tooth surface, alginate fibers swell to form a gel-like substance, a matrix for coagulation. Alginate dressings are used to pack sinuses, fistulas, and tooth cavities.[16] In recent years, much effort has been made to design composite drugs with an alginate base. A "poraprezinc–sodium alginate suspension" has been suggested as a high-performance mixture for the treatment of severe gingivostomatitis complicated by hemorrhagic erosions and ulcers. The curative effect of this drug is believed to come from poraprezinc activation of reparative processes in the mucous membranes and binding of free radicals, as well as from the haemostatic activity of sodium alginate.[17]

Dental

Alginates are widely used in the production of tooth imprints and as a matrix for plaster prostheses. The intraoral casts can be used for diagnostic purposes; dental restorative procedures; orthodontic movement of teeth; and the preparation of fillings, cups, and crowns.[18]

Surgery

Alginates are used mainly as hemostats. Gauze dressings, cotton, swabs, and special materials impregnated with a solution of sodium alginate are produced as hemostats both for external use (to cover and pack wounds and burns or to stop nosebleeds) and for application onto bleeding points during abdominal operations on parenchymatous organs. Alto, a sodium alginate drug, has somewhat more pronounced tissue adhesiveness and haemostatic effects on uterocervical hemorrhages, compared with thrombin and Francetin T.[19-23] The use of calcium alginate swabs in adenoidectomy and the internal fixation of intertrochanteric fractures of the proximal femur provided more profound hemostasis and reduced operation time compared with those times when simple gauze swabs were used.[24,25]

Gastroenterology

Mixtures of alginic acid and alginates with antacids are used to prevent gastro-esophageal reflux and to cure epigastric burning.[26-29] The administration of a pure sodium alginate suspension reduced the duration of reflux, decreased the frequency of fits, and rapidly normalized esophageal pH values in children and adolescents.[30] In testing on healthy volunteers, alginate-containing drugs, namely, Gaviscon (sodium alginate, sodium bicarbonate, and calcium carbonate) and Algitec (sodium alginate and cimetidine, an H2 antagonist), have been shown to effectively suppress postprandial and acidic refluxes[31] Moreover, Gaviscon is also capable of binding a certain amount of bile acids. When the pH equals 7, the viscosity of the drug is much greater than that of other antacids. This results in a decreased diffusion rate of bile salts and glucose and promotes a curative effect on gastro-esophageal and duodeno-gastric reflux.[32] Detoxal, a bioactive food additive containing calcium alginate, has antitoxic effects on experimentally induced tetrachlorometan hepatitis. This drug decreases the content of lipid peroxidation. Gastralgin, a drug composed of alginic acid, sodium alginate, aluminum hydroxide, magnesium hydroxide, and calcium carbonate, was recommended to treat duodenal ulcer (in clinical trials it showed curative effects in 50% to 80% of patients, ulcer epithelization, and a decrease in the relapse frequency was registered in 40% and 25% of patients, respectively).[33]

APPLICATION OF ALGINATES IN CELL CULTURE & BIOTECHNOLOGY

Recent years have shown a significant breakthrough in biomedical and biotechnological investigations on the usage of alginate gels for immobilization of viruses and living cells (bacteria, algae, fungi, yeast, and plant and animal cells).[34,35] Cell systems immobilized with alginate gels are used in ethanol production by yeast or in the production of monoclonal antibodies by hybridoma cells.[36] Alginate gels are also used as an implantation material in the creation of bioartificial endocrine glands, such as the islets of Langerhans and thyroid follicles. Because xenografts encapsulated in alginate gel are not completely protected from the immune system of the recipient, ways are found to extend the graft survival.[37] Bowersock et al suggested methods to encapsulate antigens in alginate microspheres for oral vaccination, thus providing effective local immunity against rotavirus enteric pathogens.[38] This transfer system may become a safe and cheap way for the oral vaccination of animals (and, perhaps, also man) against various infectious diseases.

Cell Encapsulation

Cells encapsulated in the alginate matrix have numerous potential applications in biotechnology.[39] Encapsulation of hormone, neurotransmitter-producing cells, or recombinant cells for the treatment of diabetes mellitus, liver diseases, parathyroid disorders, and most recently, neurological disorders, have been successfully performed.[40-46]

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Islet Cells: Animal models of transplanted islets of Langerhans encapsulated in alginate have been reported as early as 1980.[43] But it was only recently that the technology was used in humans. The first human clinical trial, which utilizes alginate as the encapsulation polymer, is accomplished with the encapsulation of pancreatic islet cells to treat patients with insulin-dependent diabetes. The transplantation was successfully performed without any adverse reactions by Dr. Soon-Shiong at St. Vincent Medical Center in 1993.[41] Ongoing investigations involve optimizing the doses of encapsulated islet cells, generation of chemically stable cross-linked alginate, and an assessment of the safety issues governing the administration of encapsulated cells to humans.

Chromaffin Cells: The work conducted by Tsang et al shows great promise in the application of the alginate microbead technology in an animal model of Parkinson's disease.[46] Dopamine, which is produced by chromaffin cells, has been shown to reverse the behavioral deficits observed in animal models of Parkinson's.[47]

Hybridoma Cells: The first successful industrial productions of monoclonal antibodies, (mAbs), from alginate poly-ε-lysine-encapsulated hybridoma cells was reported in 1985 and 1986 by Rupp and Posillico, respectively.[48,49] The method used by these two groups is an adaptation to the original work performed by Lim under the trade name of ENCAPSEL™.[50] The advantages associated with using the ENCAPSEL approach over conventional cell suspension cultures are higher starting purity of intracapsular antibody, a greater than 98% final purity level, and an overall lower cost in manufacturing production. Multigrams of high-purity mAbs from hybridoma cells can be efficiently produced using this alginate microencapsulation technology.

POROUS CARRIERS FOR BIOMEDICAL APPLICATIONS

Macroporous scaffolds are typically utilized in tissue engineering applications to allow for the migration of cells throughout the scaffold and integration of the engineered tissue with the surrounding host tissue. A method to form macroporous beads with an interconnected pore structure from alginate has been developed by incorporating gas pockets within alginate beads, stabilizing the gas bubbles with surfactants, and subsequently removing the gas. Macroporous scaffolds could be formed from alginate with different average molecular weights (5 to 200 kDa) and various surfactants. The gross morphology, amount of interconnected pores, and total void volume was investigated both qualitatively and quantitatively. Importantly, macroporous alginate beads supported cell invasion *in vitro* and *in vivo*.[51]

ALGINATE IN TARGETED DRUG DELIVERY SYSTEMS

It has been observed that alginate can be used for targeting colonic and gastric mucosa by preparation of floating beads as well as other specific organs by preparation of nanoparticles based on alginate. It has been reported that alginate beads float on a dissolution medium, and the porosity of these can be controlled by a method of drying. Thus, these can be used for targeted delivery to the stomach.[52] Floating dosage forms (FDF) can be prepared by using alginate to exhibit prolonged gastric residence, and hence, not only sustained release (SR) of drugs but also targeting to the gastric mucosa can be achieved.

Whitehead et al prepared floating alginate beads from alginate solution containing either dissolved or suspended Amoxycillin.[53] The beads were produced by a drop wise addition of the alginate into calcium chloride solution, followed by removal of the gel beads and freeze drying. The drug-release study shows that the beads prepared with the drug in solution provided some sustained-release characters, and these were improved by the addition of amylase. The beads retained their buoyancy when amylase and amoxicilline were incorporated.[54]

Desai et al have developed noncompressed controlled-release floating tablets of thyophylline using agar and mineral oil.[55] The tablets were made by dispersing a drug/mineral oil mixture in warm agar solution, and the resultant mixture was poured into tablet moulds that upon cooling and air-drying, formed floatable CR tablets. The light mineral oil was essential for the floating property of the tablet because a relatively high amount of drug (75%) and low amount of agar (2%) were used in the formulation.

Murata et al prepared two types of floating gel beads based on alginate for stomach-specific delivery.[56] In the first, vegetable oil was added to alginate beads to provide buoyancy. The model drug, metronidazole (MZ), was found to release gradually into artificial juice with the release rate being inversely proportional to the percentage of the oil. In the second, chitosan was dispersed in the matrix of alginate beads. The drug-release profile was not affected by the kind of chitosan in the beads. Serum concentration of MZ in the gastric mucosa after administration of alginate beads containing chitosan was higher than that in the solution.

Targeting Mucosal Tissues

TGF-β_1: The rapidly proliferating epithelium of the intestinal mucosa is often adversely affected by cytotoxic drugs. TGF-β_1 which is known to inhibit the growth of many cells of epithelial origin, was incorporated into alginate beads and tested in a rat model to determine its effect on *in vivo* stem cells.[57] The alginate beads contained polyacrylic acid as an excipient, which is necessary to protect the TGF-β_1 from irreversibly binding to the alginate. *In vitro* studies showed that the protein is not released from the alginate microbead when incubated in 0.1 N HCl, pH 1.0. However, when the beads were transferred to

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phosphate-buffered saline (PBS) at a pH of 7.4, all of the TGF-β_1 is released within 2 hours in an active form.[58] The acid incubation of the delivery system increases both the release rate of the TGF-β_1 and the degradation rate of the alginate beads. Both of these effects are attributed to hydrolysis of the alginate in the low pH solution. The *in vitro* studies established that the alginate delivery system is theoretically capable of protecting the entrapped protein from the harsh environment of the stomach and later releasing it at its potential site of action in the small intestine.

Vaccines: The market for effective vaccines against pathogens is large. Most commercial vaccines to date, such as mumps, childhood measles, and rubella, are currently administered via the parenteral route. Even though the conventional parenteral route of vaccine administration has proven to be ineffective in protecting individuals from airborne or mucosal-related respiratory infectious diseases, non-parenteral routes are still infrequently used.[59] The use of polymers to microencapsulate antigens has increased in recent years.[60-63] The most widely published microparticle vaccine delivery systems used to date are liposomes and poly-(lactide-co-glycolide) microspheres.[64-66] The use of other microencapsulation vehicles, such as immunostimulating complexes, cochleates, and protenoids, are also rapidly progressing.[67-69] Due to its excellent bioadhesive property and mild encapsulation conditions, alginate would seem to be an ideal mucosal delivery system for protein antigens. Ongoing studies on alginate as a vaccine delivery system showed that strong antibody responses were effectively produced when soluble antigens were encapsulated and released from poly-ε-lysine-coated alginate microbeads.[70] Intranasal administration of these ovalbumin-containing beads in mice induced high serum levels of antigen-specific antibodies of all subclasses except immunoglobulin E. Intranasal administration of unencapsulated soluble antigen mounted no antibody responses. The data also showed that administration of empty alginate microbeads evoked no immune responses, suggesting that alginate does not possess any adjuvancy properties on its own.

Kwok et al have reported the encapsulation of *Bacillus Camette Guerin* (BCG) virus in alginate microbeads.[71] The research reported the potential feasibility of delivering live BCG vaccine to the lung by either inhalation or intravenous injection. In this paper, the authors described the successful encapsulation of heat-killed BCG virus into 5- to 15-µm diameter alginate microbeads using an atomization technique.

Bowersock et al have evaluated the use of alginate hydrogels to deliver oral vaccines to different species of animals.[72] Studies from his group have indicated that alginate microbeads show great promise in delivering vaccine antigens orally to several species of animals, including rodents and cattle. Results showed that the release of the model protein ovalbumin from alginate microbeads is capable of inducing immunity at mucosal sites.

Slow-Release Applications: The controlled release of proteins from a variety of polymeric matrices has been reported. These systems are generally utilized for prolonging the circulation half-lives of proteins or for targeted delivery of proteins to specific tissues.[73,74] Alginate matrices have proven to be useful for the slow release of several potential therapeutic proteins, and several studies have demonstrated the *in vitro* and *in vivo* efficacy of these systems.

Basic Fibroblast Growth Factor (bFGF): bFGF plays a multifunctional role in stimulation of cell growth and tissue repair. This protein has a very short half-life when administered by the parenteral route and is unstable in solution. First, binding the factor to heparin-Sepharose beads developed a stable slow-release system for bFGF.[75] This permitted prolonged storage and repeated handling of the growth factor and enabled it to be encapsulated in alginate microbeads with an efficiency of 77%. Continuous release of the bFGF is demonstrated *in vitro* for more than 14 days. The release of the bFGF from the system is enhanced by the addition of heparinase to the alginate microbeads.

Interleukin-17 Receptor (IL-17R): IL-17R, a newly discovered molecule, has potential applications in the treatment of inflammatory diseases, such as osteoarthritis.[76,77] An allogeneic cell model was used to assess the effectiveness of the sustained release of IL-17R from implanted alginate beads. The single administration of alginate beads is also more convenient than the three subcutaneous injections required of the unencapsulated protein.

Leukaemia Inhibiting Factor (LIF): Austin et al have shown that the cytokine, LIF, can potentially be used for the treatment of a variety of muscle diseases.[78] The paper described the release of LIF from alginate beads for up to 80 days *in vitro*. Slow release of LIF could be advantageous because of the protein's short biological half-life.

Nerve Growth Factor (NGF): Reduced production of NGF has been implicated in age-dependent cholinergic neuronal atrophy and neuronal degeneration of the forebrain.

Maysinger et al tested the suitability of alginate for the microencapsulation of NGF.[79] The authors described the advantages associated with using this alginate technology, which include ease of administration and the protection of NGF from hydrolytic cleavage. The study indicated that the release of encapsulated NGF could prevent neuronal degeneration in the rat model for central cholinergic degeneration

Interleukin-2 (IL-2): Recently, alginate microspheres have been used as a matrix for the delivery of IL-2.[80] Three types of microspheres were prepared by first dissolving sodium alginate in distilled water at a concentration of 2% (w/v). The solution was then spray-dried into a 0.5% $CaCl_2$ solution. After curing for 10 minutes, the microspheres were placed in coating solutions of: (1) chitosan hydrochloride; (2) poly-ε-lysine; or (3) $CaCl_2$. The IL-2 was incorporated into the preformed microspheres by diffusion from an external aqueous solution of IL-2. *In vitro* sustained release of IL-2 from the alginate-chitosan system is found to last for 5 days, and IL-2 is completely recovered

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from the matrix. The *in vitro* activity of the released IL-2 was investigated by determining the induction of cytotoxic T lymphocytes (CTL) when incubated with tumor cells and lymphocytes. The IL-2 remains active in the alginate-chitosan microspheres and is more efficient in triggering the induction of CTL than free IL-2.

DNA Encapsulation

With recent advances in the field of gene therapy, new methods to efficiently deliver DNA oligonucleotides are being evaluated. There are two studies to date that report the potential application of alginate as an enteric delivery vehicle for DNA.[81,82] The encapsulation of DNA and its derivatives may be used in enteric targeting of nucleic acids as gene transfer agents, modified oligonucleotides, and carriers for DNA-intercalators. *In vitro* studies showed that DNA could be successfully encapsulated and released at pH 6.5 without any denaturation of the DNA molecule. Alginate-chitosan encapsulated DNA can be used as a target or carrier for evaluating intestinal carcinogens.

Microsphere & Liposome Encapsulation

Alginate gels have been used to encapsulate other delivery systems, including microspheres and liposomes. Ethyl cellulose microspheres were dispersed into an aqueous solution of sodium alginate, which was subsequently dropped into a $CaCl_2$ solution.[83] The authors suggested that the beads could potentially be useful as an oral delivery system for micro- or nanoparticles. Liposomes that contained the model proteins BSA or horse-radish peroxidase were incorporated into alginate spheres with a diameter of 500 to 800 µm.[84,85] Prior to their entrapment, the liposomes were coated with either phospholipase C, D, or A_2. The alginate microbeads that contained the liposomes remain stable at 10°C. Upon heating to 37°C; release of the protein is triggered by the enzymatic degradation of the phospholipids by the phospholipases. By selecting the appropriate phospholipase, the duration of protein release could be controlled.

Alginate Particulates as Carriers for Controlled Delivery

Alginate has been used as a carrier for controlled drug delivery of acid-sensitive and gastric-irritating drugs, drugs of different solubility, drugs of different ionic groups, macromolecular drugs, and drugs for hyperlipidemia. Yotsuyanagi et al reported that alginate gel particles show a pH-sensitive swelling property, ie, the particles remain unchanged in distilled water or acidic medium (pH 1.5 KCl-HCl) but swell rapidly in pH 7.0 phosphate buffer to a size greater than the original size.[86] This property of alginate can be useful for drugs that are acid sensitive because they can be shielded from attack of gastric juices and can be released at a desirable rate in the intestine because of reswelling of xerogels in the intestine.

Hwang et al incorporated ibuprofen in alginate beads.[87] This offers the advantage of avoiding gastric irradiation caused by ibuprofen because not much of the drug is released in the acidic pH of the stomach.

Reynolds et al has used alginate as a controlled-release carrier for drugs of different solubility, ranging from freely water-soluble drugs, such as vancomycine, timolol maleate, ascorbic acid, and metoclopramide hydrochloride, to practically water-insoluble drugs, such as indomethacin, furosamide, and dipyridamole etc.[88]

Bodmeier and Wang et al prepared sustained-release polymer particles containing drugs with various solubility characteristics (ibuprofen, theophyllin, guaifenesin, and pseudoephedrine HCl) based on alginates with colloidal polymer dispersions.[89]

Liu and Krishnan et al prepared drug delivery particles by using alginate; polylysin and pectin, theophyllin, chlorthiazide, and indomethacine were used as model drugs.[90] Alginate and pectin serve as core polymers, and polylysin helps strengthen the particulate. In the acidic solution, only the water-soluble drug, theophyllin, was released from all three particulates. Chlorthiazide was released only from the alginate particles in 0.1 N HCl. For the least-soluble drug, indomethacin, the amount of drug release from the three particles was far less than their t_{50} and t_{90} values. In alkaline solution, pH 7.5 plain alginate particulates were able to control the release of soluble drug (theophyllin) beyond 1 hour (pectin-polylysin particulates achieved t_{90} at 3.5 hours).

Osrberg et al studied properties of Ca-alginate matrices in various media.[91] Three drugs of different solubility were chosen, and their release rate was investigated in 0.1 N HCl and water. Only when pure water is applied as a release medium, the matrices were able to extend release of two least-soluble drugs, theophyllin and chloramphenicol. In all other media, the release proceeded much more rapidly due to the various transformations in the carrier material.

Murata et al prepared calcium alginate beads containing chitosan salt using nicotinic acid, a drug for hyperlipidemia.[92] These were shown to release nicotinic acid in diluted HCl solutions (pH 1.2) and in physiological saline. When placed in bile acid solution, it took bile acid into itself. Therefore, this could be used for hyperlipidemia. Alginate beads containing chitosan are useful because when administered orally, they bind to bile acids in the small intestine like cholestyramine and hence decrease plasma cholesterol and can be used to prevent hyperlipidemia.

Shiraishi et al reported that alginate beads could be used for controlled release of indomethacin.[93] The drug, however, does not release at pH 1.2 because of its low solubility in aqueous medium; it releases at pH 6.8 due to swelling of alginate at this pH.

Riberio et al studied microencapsulation of lipophilic drugs in chitosan-coated alginate microspheres.[94] The slower rate of release from coated microspheres is suitable as a delivery vehicle for oil-soluble drugs.

Hwang et al prepared excipient-loaded alginate gel beads and found that the release of ibuprofen could be controlled by adding excipitients.[95] The release of ibuprofen from alginate beads at pH 6.8 was more rapid than at pH 1.2. Ibuprofen was released at pH 1.2; whereas almost 100% of ibuprofen was released at pH 6.8 for 8 hours. The release rate of ibuprofen at pH 6.8 is found to increase upon

addition of excipients.

Floating dosage forms that demonstrated favorable *in vitro* floating characteristics was developed. Only a slight difference was noted between drug release profiles of non-compacted and compacted alginate and alginate-HPMC microspheres. Although dentation and distortion of microspheres was observed with increasing compaction pressure, the microspheres generally remained intact with minimal rupture/fracture.

OTHER APPLICATIONS OF ALGINATES AS DRUG EXCIPIENTS

Many drug substances have a bitter or unpleasant taste that makes them unsuitable for certain oral dosage forms. Sodium alginate has been used in tablets to mask the bitter taste of amiprilose hydrochloride as a model drug. A core tablet was undercoated with sodium alginate and over coated with calcium gluconate in order to form a gel on the tablet surface in the mouth at oral administration. The method was found useful for taste masking of oral compressed formulations.

SUMMARY

The overall annual growth rate for alginates is 2% to 3%, with textile printing applications accounting for about half of the global market. Pharmaceutical and medical uses are about 20% by value of the market and have stayed buoyant, with 2% to 4% annual growth rates, driven by ongoing developments in controlled-release technologies and the use of alginates in wound care applications. Food applications represent about 20% of the market. That sector has been growing only slowly, and recently has grown at only 1% to 2% annually. The paper industry represents about 5%, and the sector is very competitive, not increasing but just holding its own. The result is low profitability for most of the industry, with the best opportunities lying in the high end of the market, such as pharmaceutical and medical applications. ◆

REFERENCES

The 95 references are available upon request; please contact Dan Marino at dmarino@drugdeliverytech.com.

BIOGRAPHIES

Mrs. Geeta Patel earned her MPharm from the S.K. Patel College of Pharmaceutical Education and Research, Ganpatvidyanagar, Kherva, Gujarat, India. Presently, she is persuing her PhD in Pharmaceutics and Pharmaceutical Technology and is working as a lecturer at the same college. Her research activities focus on preparation and evaluation of novel vaginal drug delivery systems. She has 5 publications and 8 presentations to her credit.

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ADVANCED DELIVERY DEVICES

Specialty Medical Devices Enabling Better Patient Care

By: Chris Halling, MCIM

INTRODUCTION

It is becoming clear, that in many cases, patient compliance can be better assured with assistance from within the device itself. Bespak, a global player in the design, development, and manufacture of specialty medical devices, believes that in time, more and more regime assurance and assistance features will be incorporated into everyday drug delivery devices. It is becoming a regulatory requirement for certain features to be included and, as recently as 2001, the US FDA issued a draft guidance recommending that dose counters be considered for all future MDI therapies. This discussion reviews the progress to date of dose counting and other technologies that will aid compliance, such as regime assurance devices and new MDI valve designs that allow patients to comply with their medication regime more easily. It will also review other recent delivery device developments, in particular, delivery via the nasal route, reviewing how these advancements have given pharmaceutical partners a unique point of difference and ultimately, how these other routes of administration may help patients comply more easily with their dosing regime.

THE EVOLVING ROLE OF DRUG DELIVERY DEVICES

As drug development costs continue to spiral and the generic therapies market becomes more competitive, the business case for developing devices that enable the non-invasive delivery of drugs and provide a competitive advantage through a tangible patient compliance benefit is becoming increasingly obvious.

For some years, device manufacturers have focused on developing additional patient features for Metered Dose Inhalers (MDIs) in order to offer a credible alternative to Dry Powder Inhalers (DPIs). This is partially because of the relative ease of formulating combination therapies as stable powders and partially because many systemic therapies have initially been formulated as such. DPIs have progressed in design relatively rapidly whilst the bulk of development work on MDIs has been focused on reformulation using more ozone-friendly hydrofluoroalkane (HFA) propellants. Though there is evidence to suggest that MDI technologies offer real benefits in terms of cost effectiveness and speed through regulatory compliance to market, there remains some lag in the development of the latest therapies in MDI form. This is partly due to concerns that MDIs remain difficult for some patient groups to use, and this perception is enforced by the need for two-shot dosing and a lack of effective dose counting. Modern DPIs do offer much sought-after design and patient compliance features not offered by MDIs, but they are relatively expensive and still require some user training to be effective. The increasing potential to use the lungs as an access route to the systemic circulation may necessitate a change in basic inhaler design, but particularly MDIs. It is estimated that by 2010, pain relief and other systemic drugs will account for up to 5% of the MDI market, and with more expensive therapies being delivered, the need to assist patients and prescribers to use the device correctly will become even greater.

DEVELOPMENTS IN VALVE TECHNOLOGY

It can be argued that the most impactful technologies are those that provide a benefit invisibly and do not require the user to consider more information or learn further steps to gain advantage. If you accept this point of view, then one of the most impactful regime assurance solutions lies within a part of the MDI that few patients ever see. The development of a MDI valve that guarantees a full dose with each actuation is a significant advance. Because of the internal design of conventional MDI valves, an inhaler may require "priming" when it has been left inverted for a period of time or even shaken while being carried around. This is because conventional MDI valves fill a metering chamber immediately after the last dose is fired, and this chamber may partially empty if the inhaler is inverted or left. For the inhaler to then deliver an optimum dose, the patient should

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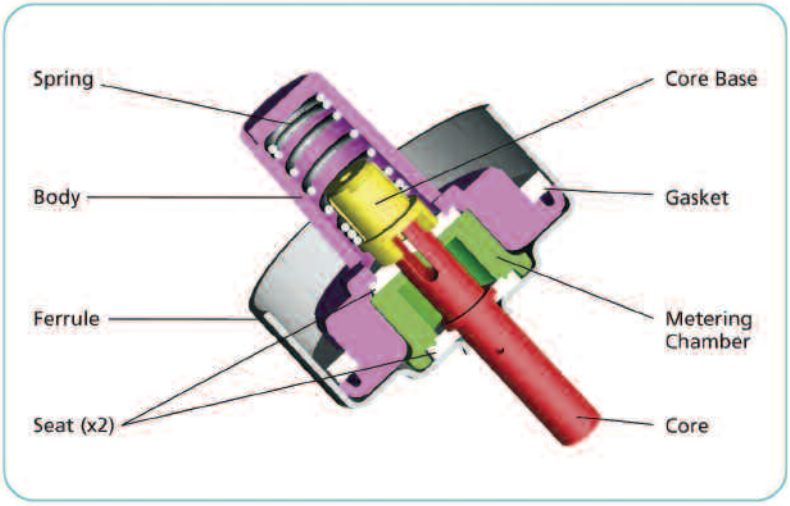
FIGURE 1



ideally fire one shot into the air to ensure the valve chamber is completely refilled from the main can reservoir. This requirement results in high levels of wastage and of course assumes that the patient has been shown how to use the inhaler properly or has read the easily ignored Patient Information Leaflet that came with their medication. Of course, this is often not the case, so the only reliable method to ensure a full dose is to recommend a regime based on two puffs from the inhaler. Because the Easifill valve (Figure 1) requires no priming, pharmaceutical partners can provide a drug delivery solution that gives a consistently accurate dose with a single actuation, resulting in greater regime compliance as patients need only take one puff of their inhaler rather than the two usually recommended. This also reduces waste and, with the growing likelihood of more expensive molecules being delivered from MDIs, will almost certainly offer a significant economic advantage.

The valve also improves accuracy in dosage delivery as the core has been designed to provide an open channel in/out of the chamber in the at-rest position. This ensures that there is no flow of formulation back into the chamber, no chance of sediment settling within the body of the valve, therefore reducing the metering chamber volume and hence the next dose.

ENHANCED ACTUATORS

Many patients find it difficult to coordinate the firing of their MDI with the correct point of inhalation. This is made more difficult when the medication feels uncomfortable on the back of the throat and may even cause a gagging effect. Developments in the design of actuators, notably the use of actuators with smaller orifice diameters that produce a much slower, "warmer" spray make it easier for the patient to coordinate inhalation and therefore better ensure that the correct dose is administered to the correct part of the respiratory system.

CREATING COST-EFFECTIVE DOSE COUNTERS

Dose counters enable patients to track the amount of medication they have remaining in their inhaler and aid compliance by reducing the likelihood of enforced breaks in the regime. This is brought about when a patient finds his/her MDI is empty but cannot immediately get a replacement. Bespak has a deep understanding of the interfaces and tolerances critical to accurate dose counting. Researchers at the company have been able to develop a cost-effective mechanical dose counter (Figure 2) taking care to ensure the device will never under-count and therefore never suggest there is a dose remaining in an empty inhaler (the consequences of which clearly could be dire for a patient suffering from an asthma attack). Bespak has opted for a simple design with few components so that high volumes can be manufactured using automatic machinery, a critical consideration if dose counters are to be universally adopted for low-cost or generic therapies.

Current designs have been very much developed with both the patient and prescriber in mind, with mooted features including a removable, washable spray nozzle, a clear plastic outer casing so the canister information can be seen by both parties, and a security feature that means the canister cannot be removed from the device. This means that the counter never shows an error because the pack has been changed, ie, a half-empty drug pack exchanged for a full one. Further refinements, including an anti-fire feature to prevent accidental discharge, are currently in development.

THE CHANGING ROLE OF MDIS

As already stated, the expectation is that MDIs, though still a robust delivery mechanism in the treatment of asthma, will be increasingly utilized in pain relief and for other systemic therapies. For example, severe pain management may require the administration of controlled substances, such as opioids, but only within certain pre-set limits. The consequences of over-dosing on these more powerful drugs may be far more

FIGURE 2

severe, and the risk is greater too as patients may be disorientated through the use of other medications or be suffering such severe pain that they will take too much of the potentially lethal therapy. There is also the risk of accidental misuse or deliberate abuse. In order to mitigate such risks, MDI design concepts have been developed to improve their safety and security.

Incorporated into the MDI device itself, a Regime Assurance Device (RAD) can prevent access at "non-administration" times, which not only helps patients comply with the prescribed regimen, but also enables prescribers to monitor usage and, of course, prevent easy access by unauthorized users.

Audible and/or visual reminders have been incorporated to provide patients with information on when the last and next dose should be administered. This feature has real benefits; particularly where preventative medication is being prescribed and there is a real risk patients will simply forget to take their medication because they are not experiencing any symptoms. The RAD design also incorporates a dose counter and is breath-actuated, removing the need for a patient experiencing discomfort or suffering disability to then have to coordinate the actuation with inhalation.

Helping patients to comply with their dosing regime is often about providing an appropriate alternative to the needle. Device developers have a role to play in devising the enabling technologies for pharmaceutical developers to accurately and reliably target other areas of the body like the lung or the nasal passages. Through an in-depth understanding of the relationship between the three key components of nasal drug delivery, namely: the formulation, the anatomy of the nose, and the characteristics of the delivery device, drug delivery companies are now able to manufacture complex nasal devices for a whole range of formulations. Bespak has successfully combined its own knowledge of device development with computer models that predict deposition in the nose. By varying particle size and even the exact point in the nostril where particles are released, Bespak has been able to demonstrate the more efficient targeting of certain areas in the nose. This may be useful when administering systemic therapies to the highly vascularized nasal turbinates or in avoiding certain areas, such as the olfactory region.

SUMMARY

The demands placed on modern device manufacturers to deliver even greater compliance aids will inevitably increase in the coming years as organizations look to deliver more systemic therapies. The breadth and depth of regime assurance features is substantial and as technology evolves, the cost effectiveness of such features will make them more accessible and desirable to pharmaceutical companies. It is however essential that the advanced functionality is both discrete and easy to operate. The overall design of any regime assurance device should not stand out from the traditional MDI and therefore become too cumbersome, complicated or, if controlled substances were to be delivered, a recognizable target for would-be abusers. The device should be developed from the patients' perspectives, though clearly any technology should be able to be manufactured in sufficient numbers with sufficient ease to prevent it from being cost-prohibitive. Developments in valve technology, particularly the Easifill valve, can be incorporated into new MDI designs relatively easily and offer immediate benefits in terms of patient compliance. Other technologies perhaps require a greater degree of planning and assessment and do increase the cost of the device. That said, the benefits to the patient and the savings in terms of wasted formulation might well outweigh that cost. ◆

BIOGRAPHY

Mr. Chris Halling joined Bespak as Marketing Manager in January 2001 and has been responsible for all aspects of marketing, including research, strategy, and communications. As the Bespak group grew to incorporate a US manufacturer of anaesthesiology equipment, he was promoted to Head of Corporate Communications in November 2006. Prior to joining Bespak, he held positions as UK and overseas product manager at Foster Refrigerator, the UK manufacturer of commercial refrigeration equipment. Mr. Halling holds a post-graduate degree in Management Studies from Anglia Polytechnic University, Cambridge, is a recently graduated six-sigma greenbelt, and a member of the Chartered Institute of Marketing.

LIFECYCLE STRATEGIES

Drug Delivery is Integral to Lifecycle Strategies

By: Frost & Sullivan Analyst, Jason McKinnie, MPH

INTRODUCTION

Effective strategies in product lifecycle management can substantially benefit companies by adding additional years of branded drug revenues. The patent life for pharmaceuticals is significantly decreased from other industries, including those in healthcare, because of the lengthy research and clinical evaluation process for drugs. These unique pressures facing the pharmaceutical market require companies to utilize innovative product lifecycle management strategies to maximize revenue and extend revenue production past patent expiration. There are four common strategies companies use to achieve this goal: addition of new indication, single-pill combinations, next-generation, and changing drug delivery.

Changing the drug delivery method can play an integral role in all product lifecycle management strategies. Loosely defined, changing the drug delivery method can be incorporated in all, because changing a once-a-day pill to a once-a-month pill requires new delivery technology. Strictly defined, changing drug delivery is the route of delivery, such as shifting from a nasal spray to a pill or from an injection to a pill. For the purposes of this article, any change of drug delivery is applicable because many of the new technologies drug delivery companies are working on entail significant improvements in oral, nasal, inhaled, and injection therapies that would improve older drugs even if delivered by the same physical mechanism.

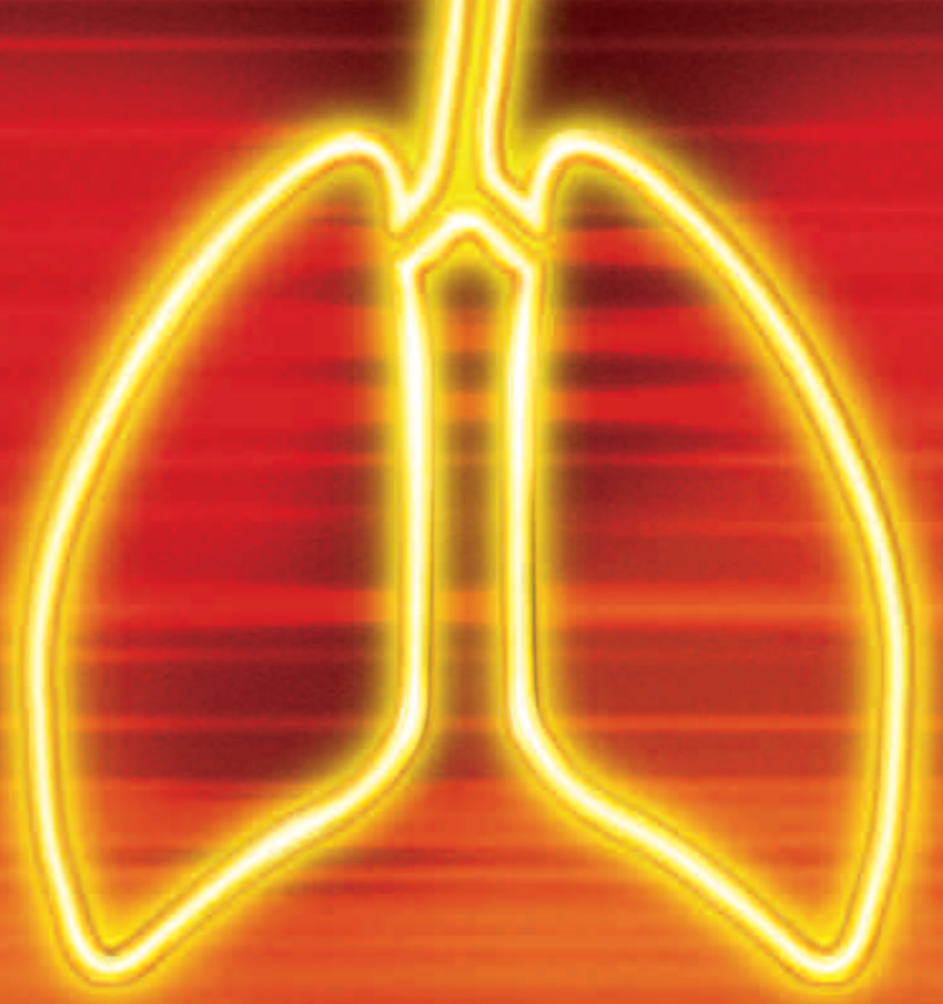
MULTIPLE DRUG DELIVERY SPURS PRODUCT SUCCESS

The classic and arguably the best example of a company utilizing multiple drug delivery technologies is GlaxoSmithKline for its drug franchise Imitrex. First approved by the FDA in December 1992, the injectable drug provided much needed relief for migraine sufferers. The company understood its patients and knew that injectable delivery is the least desirable method of drug delivery, and therefore developed an oral formulation that was approved in June 1995. The company did not stop there, knowing that not all its patients were adequately treated. Many migraine patients also suffer from nausea, preventing them from taking an oral formulation. To serve patients who suffered from nausea and did not want injection-based therapy, the company developed a nasal formulation that was approved in August 1997. The drug has benefited from a long patent life, but the flexibility of three different drug delivery options helped Imitrex maintain market leadership in the multi-billion dollar migraine market.

The leadership GlaxoSmithKline developed in Imitrex has been copied by the other major companies in respect to migraine products. Most companies with migraine drugs on the market offer two different delivery methods. GlaxoSmithKline pioneered the strategy of changing drug delivery and became a role model for competitors in the process.

Roche Pharmaceuticals is utilizing multiple drug delivery options in the highly competitive osteoporosis market. Boniva was first approved as a once-daily pill in May 2003. Shortly after that, the company developed a once-a-month pill version and sought FDA approval. Ten months after submission, the FDA granted approval to the once-a-month version of Boniva in May 2005. The company further developed the drug into an injection delivered every 3 months and was approved in January 2006. The three different options for Boniva set it apart from other drugs in the market and have helped it garner a 15% market share despite only being on the market for a short time.

Abbott Laboratories has translated successful drug delivery changes into substantial revenues through continued advancement of its cholesterol drug TriCor. After obtaining the license for its approval, the company only had 4 years before generic entry could erode its sales. In 2001, the company received approval for a second-generation TriCor, which lowered the dosage through more efficient oral drug delivery. The lowered dosage also helped decrease the potential for side effects. The company again avoided generic erosion in 2005 by releasing a third version of TriCor



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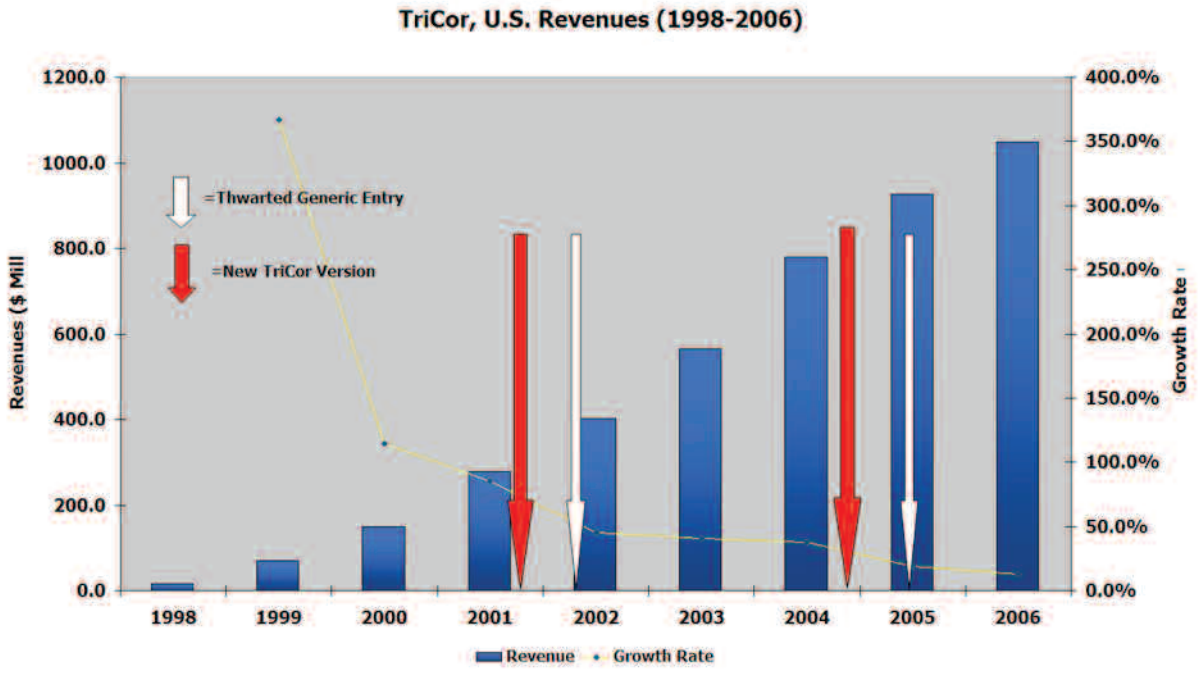

that was more technologically advanced. Through novel nanobiotechnology manufacturing developed by Elan Corporation, the third-generation TriCor no longer needed to be taken with a meal. These enhancements in drug delivery, though all still oral, significantly improved the product lifecyle of TriCor and prevented generic entrants two different times. Figure 1 highlights the revenue TriCor has generated since its approval.

ADVANCES IN DELIVERY TECHNOLOGIES

Expenditures in research and development have increased significantly in the past 20 years with some of that focus going toward drug delivery. Many companies now analyze drug delivery at the earliest stages of development and attempt to focus their efforts on the best method for that drug. Neither the intense level of scrutiny nor technological advances were consistently available to companies until the mid 90s, which has resulted in numerous drugs on the market that have not undergone an intense analysis of drug delivery. Technological advances in nasal, inhalation, injectable, oral, and transdermal delivery are enabling older drugs as well as new drugs to be effectively delivered through multiple routes of administration.

Transdermal drug delivery entered into a new era with the approval of IONSYS, the active fentanyl patch from Ortho-McNeil, a subsidiary of Johnson & Johnson. Active patch delivery uses an external energy source to facilitate transfer of molecules. Active transport, using other methods of external delivery being developed by other companies, could potentially be used for proteins and other large or water-soluble molecules. Other technological advances in the traditional passive patch design, such as DOT-Matrix from Noven Pharmaceuticals, are facilitating molecules never used before in transdermal drug delivery. Pain medications and hormone treatments were the predominant indications for transdermal, but the improved patch technology is allowing uses for vaccines, neurological disorders, and other lifestyle indications.

Nasal drug delivery technology is expected to substantially improve in the next several years as devices are used to deliver drugs to the nasal mucosa. Spray pumps are presently the industry standard for nasal drug delivery but have always been inefficient at depositing the drug where it's needed and also contributes to a large amount of post nasal drip. This inefficiency at drug delivery has discouraged many drug makers from utilizing the nasal mucosa as an alternative to injection and oral therapies. New devices from Kurve Technology and OptiNose are hoping to

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alleviate these concerns and attract drug makers to use their device to deliver a wide-ranging assortment of molecules, not just the corticosteroids that presently dominate the market.

The inhalation drug delivery market has already shown some advances in delivery technology. Whereas the metered dose inhaler was the standard in the 1980s, newer devices began entering the market. Metered dose inhalers no longer use CFCs as propellants, and some companies have done away with the propellant completely. The use of dry powder inhalers have allowed for more controlled delivery. The next stage of delivery advances are with the devices currently being tested for the delivery of insulin. Exubera, developed by Nektar Therapeutics and marketed by Pfizer, has allowed the delivery of a protein through the lungs. Other companies, such as Alkermes, are following suit.

The oral therapy market has undergone substantial changes in delivery technology, allowing companies to significantly reduce the number of daily dosings through enhanced solubility and sustained release. Nanobiotechnology is an exciting application for all forms of drug delivery, and it is having a substantial impact on the way drugs are being manufactured. The advent of this technology has enabled companies to significantly change an older oral version of a drug into a new oral version. Additionally, companies are continually researching the ability of utilizing oral formulations to deliver proteins and other large molecular weight compounds.

PIPELINES BEGINNING TO SHOW INCREASED DRUG DELIVERY DEVELOPMENT

Alcon Laboratories has marketed the antihistamine eye drop Patanol since its approval in December 1996. The company, after learning of its potential for treatment of nasal allergies, developed the active ingredient into a nasal spray and is expected to seek approval in 2007. This potential new indication is expected to help lengthen the product lifecycle by creating a new indication through modification of its drug delivery.

Schwarz Pharma has developed a drug to treat Parkinson's disease and has simultaneously developed two methods of delivery. The transdermal version of the drug was approved in Europe in January 2007, while the nasal version is in Phase II development. The company hopes to use the patch to treat symptoms of Parkinson's disease, while the nasal formulation will be used for acute symptoms. The utilization of two delivery methods is expected to help the company gain market share in this growing market.

SUMMARY

Drug delivery technologies are constantly undergoing changes and improving to help patients comply with their doses. Additionally, companies now have adequate choices when determining the most successful route of delivery along with dosage strategies. The 10-month approval process for the once-a-month dosage of Boniva shows the FDA has the ability to quickly approve a drug that has undergone modification of delivery. If companies do not look to improve upon the delivery of their branded drugs, generic erosion will limit revenues. With increasing competition and R&D costs, companies need to utilize all strategies available to protect their product's lifecycle, and changing drug delivery has shown to be an effective strategy.

BIOGRAPHY

Mr. Jason McKinnie is a Pharmaceutical Research Analyst for Frost & Sullivan in the Healthcare and Life Sciences division. He primarily works in the emerging cancer therapeutics industry, providing insight into pipeline analysis, market forecasts, and industry trends. Mr. McKinnie has worked studies involving emerging cancer therapeutics, which includes creating and distributing surveys with oncologists around the US and conducting interviews with key industry participants. He came to Frost & Sullivan with extensive scientific research in biochemistry in both the academic and industry realm. In addition to his research background, he brings with him real-world healthcare knowledge through his work in a cardiology lab and through his graduate education. Mr. McKinnie graduated in 2004 with a Master of Public Health from Texas A&M University Health Science Center School of Rural Public Health and also earned a BS in Genetics from Texas A&M University.

PROTEIN PRODUCTION

Animal Pharming for the Production of Pharmaceutical Proteins

By: R.P. Patel, MPharm; M.M. Patel, PhD; and N.A. Patel, MPharm

ABSTRACT

Animal pharming, the process of using transgenic animals to produce human drugs, is staking its claim in a lucrative world market. In comparison to traditional approaches of pharmaceutical protein production, the protein produced by transgenic animals is likely to be more biologically active, cost effective, and safe. However, numbers of scientific, technical, legal, social, commercial, environmental, and ethical challenges exist. Producing transgenic animals is still relatively expensive, however, overall cost of producing protein is trending down, and transgenic animals have certain advantages over traditional laboratory methods for producing human proteins.

INTRODUCTION

Advances in scientific discovery and laboratory techniques in the past half of the 20th century resulted in the ability to manipulate the deoxyribonucleic acid (DNA) of organisms and gave rise to transgenic animals. The use of transgenic animals may accelerate classical breeding programs and provide a means for the economical production of life-saving pharmaceuticals.[1]

Transgenic animals are animals that have been genetically transformed by splicing and inserting foreign animal or human genes into their chromosomes. The inserted gene, when successful, enables an animal to make a certain pharmaceutical protein in its milk, urine, blood, sperm, or eggs, or to grow rejection-resistant organs for transplant.[2]

While this idea may not be that new, its implementation is just now beginning to take shape. Numerous companies are springing up all over the world marketing a plethora of these pharmaceutical products. With our current knowledge of what affects embryonic development being limited, the major hurdle to the success of these products is the ethical issues that have arisen through the use of transgenic animals, especially if they are to be used for human consumption. Recent developments in reproductive technology have brought cloning technology and the issue of human cloning to the forefront.[3-6]

SIGNIFICANCE OF TRANSGENIC ANIMALS

Automated gene sequencing and the biological advantages of animals, when compared to more traditional methods of recombinant protein production, have combined to make pharming a preferred alternative. Traditional methods of recombinant protein production use laboratory cell cultures of transgenic bacteria, yeast, or animal cells to produce proteins.[7] Inherent disadvantages in traditional methods, when compared to using animals as bioreactors, include (1) cell and bacterial cultures require constant monitoring and sampling; (2) expansion is more costly because substantial plant machinery must be purchased and maintained; (3) in order to retain biological activity, many proteins require modifications (addition of sugars, for example), some of which are only performed by mammalian cells; and (4) isolating and purifying proteins is more difficult than purifying proteins from an animal's milk or bodily fluid.[2]

So, even though the initial cost of producing transgenic animals is quite high, using animals as bioreactors is actually a cost-efficient alternative to mass produce human pharmaceuticals. Overall, animals as bioreactors are more cost effective because the product is efficiently passed through the milk, with an average yield of 53% and with 99% purity. The purifying process may become more simple if harvesting proteins from poultry eggs and urine becomes viable.

Using animals as bioreactors is also cost effective and advantageous because animals naturally carry the cellular mechanisms needed to produce complex proteins. Genes require certain cellular mechanisms to help them produce proteins. These mechanisms are present in a living animal, but they may be difficult or impossible to replicate in a cell culture.[2]

Transgenic animals serve as an important production facility for the

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secretion of valuable proteins in milk. Many active human proteins contain carbohydrate or lipid side groups that are added post-transcriptionally. Because bacteria do not contain the enzymes that catalyze the addition of these important groups, the functionality of the recombinant proteins is compromised. In response, it is wise to explore alternative methods for producing biologically active human proteins. Transgenic animals can be used to produce human proteins for pharmaceutical uses in various body fluids like milk, blood, urine, and semen from where they can be extracted and purified.

Production of transgenic animals to obtain pharmaceutical proteins offers a number of advantages, eg, recombinant isolated genetic sequence of a human therapeutic protein produced by the transgenic animals is identical to the human and hence there are no opportunities for ADRs (adverse drug reactions). Another significant advantage, which encourages such application, is the yield, which is considerably high and can be increased by constructing a transgene, which is required to be inserted into the genome of new animals.

There are already reports indicating the successful production of the expression of the protein in milk of transgenic animals in sheeps, pigs, goats, cows, and chickens (Table 1).

TABLE 1

Animal	Drug/Protein	Use
Sheep	alpha1 anti-trypsin	deficiency leads to emphysema
Sheep	CFTR	treatment of cystic fibrosis
Sheep	tissue plasminogen activator	treatment of thrombosis
Sheep	factor VIII, IX	treatment of hemophilia
Sheep	Fibrinogen	treatment of wound healing
Pig	tissue plasminogen activator	treatment of thrombosis
Pig	factor VIII, IX	treatment of hemophilia
Goat	human protein C	treatment of thrombosis
Goat	antithrombin 3	treatment of thrombosis
Goat	glutamic acid decarboxylase	treatment of type 1 diabetes
Goat	Pro542	treatment of HIV
Cow	alpha-lactalbumin	anti-infection
Cow	factor VIII	treatment of hemophilia
Cow	Fibrinogen	wound healing
Cow	collagen I, collagen II	tissue repair, treatment of rheumatoid arthritis
Cow	Lactoferrin	treatment of GI tract infection, treatment of infectious arthritis
Cow	human serum albumin	maintains blood volume
Chicken, Cow, Goat	monoclonal antibodies	other vaccine production

Pharming Products Currently in Development[2]

PRODUCTION OF PROTEIN IN MILK

Advanced Cell Technology, Inc is using the queen of milk production, the cow, for potential use as bioreactors.[7] They have produced transgenic cows that secrete the protein serum albumin in their milk, a protein that is used to extend blood volume and in patients suffering from traumatic injuries, such as burns. Cows are an obvious choice for pharming purposes as they can produce upward of 8000 L of milk per year, and an estimated 40 to 80 kg of protein a year. That is quite a substantial amount compared to the 4 kg of protein per year in goats and 2.5 kg of protein per year in sheep.[7]

PRODUCTION OF PROTEIN IN OTHER BODY FLUIDS

Pig semen is also being investigated as a protein source by genetic engineering of the seminal glands because pigs (male) produced large amounts of seminal fluids (approx. 200 to 300 ml per ejaculate, containing 30 mg of normal protein per ml), and boars can ejaculate 2 to 3 times a week year round. Semen could be extracted from the transgenic boars daily.

Not only the milk and semen, but also such proteins can be produced in other biological fluids, such as urine, saliva, and blood by utilization of tissue-specific promoters that target the following:

1. Urine, such as uroplakin;
2. Saliva, such as epidermal growth factor (EGF) promoter, and
3. Blood, such as hemoglobin or serum albumin greatly enhanced our ability to use these fluids for protein production.

Large quantities of material can be

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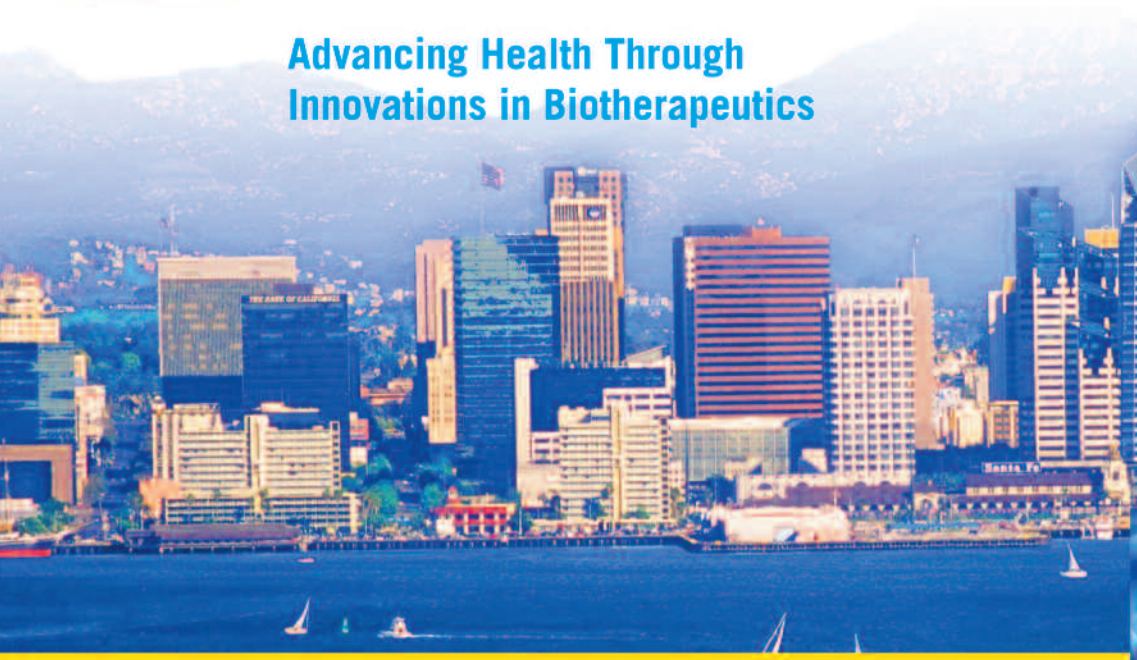

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TABLE 2

	Traditional Cell Culture	Poultry Eggs	Goat Milk
Raw Material Volume (kg)	170,000	250	21,000
Capital Equipment Cost, or Cost Per Animal (dollars)	100 Million	1,000	10,000 to 50,000
Equipment Maintenance Costs, or Keeping Cost Per Animal (dollars)	100,000	10	2,500
Unit Cost Per Protein (dollars per gram)	100	0.10 to 0.25	2 to 20
*100 kg of raw material per year			

AviGenics Comparision of Production Inputs & Costs for Monoclonal Antibodies* Using Cell Culture Versus Trasgenic Poultry or Goats[9]

produced in these fluids from livestock species including horses and in poultry.

COST COMPARISION

Unit cost per protein should be significantly less when animals are used as bioreactors to produce human proteins. Only a fraction of the raw material, capital equipment, and maintenance costs needed for traditional cell culturing are required with transgenic animals. Table 2 highlights one private firm's estimates regarding the superiority of transgenic human protein production through eggs or goat milk.

In addition to lower costs, transgenic technology provides an ideal route for bulk production because very high expression levels of fully bioactive proteins are obtained. The success of the mammary gland bioreactors lies in the capability of the alveolar epithelium to provide appropriate post-translational modifications to proteins so that they take on their biologically active form. When full post-translational modification of protein is not accomplished, biological activity is compromised. For some important proteins (eg, protein C), traditional technologies (mammalian cell culture and bacterial fermentation) are unable to process such complex proteins as successfully as the transgenic processes. Because post-translational modifications are not efficient in other systems, the bacterial fermentation volume required to provide a comparable amount of active protein from mammalian cells is much larger.

PRODUCING TRANSGENIC ANIMALS

Gene transfer approaches to produce transgenic animals include using retro/adeno and other viruses, pronuclear microinjection, ES cell/EG cell exposure to foreign DNA, SMGT (Sperm Mediated Gene Transfer), electroporation, liposome-mediated gene transfer, biolistics (gengun), NT (Nuclear Transfer) with somatic cells/ ES/EG cells, and other modern approaches.

Through genetic engineering, the DNA gene for a protein drug of interest can be transferred into another organism for production. Which organism to use for production is a technical and economic decision. For certain protein drugs that require complex modifications or are needed in large supply, production in transgenic animals seems most efficient. The farm animal becomes a production facility with many advantages — it is reproducible, has a flexible production capacity through the number of animals bred, and maintains its own fuel supply. Best of all, in most animal drug production, the drug is delivered from the animal in a very convenient form — in the milk.

A transgenic animal for pharmaceutical production should produce the desired drug at high levels without endangering its own health, and pass its ability to produce the drug at high levels to its offspring. The current strategy to achieve these objectives is to couple the DNA gene for the protein drug with a DNA signal directing production in the mammary gland. The new gene, while present in every cell of the animal, functions only in the mammary gland so the protein drug is made only in the milk. Because the mammary gland and milk are essentially "outside" the main life support systems of the animal, there is virtually no danger of disease or harm to the animal in making the "foreign" protein drug.

After the DNA gene for the protein drug has been coupled with the mammary directing signal, this DNA is injected into fertilized cow, sheep, goat, or mouse embryos with the aid of a very fine needle, a tool called a micromanipulator, and a microscope. The injected embryos are then implanted into recipient surrogate mothers in which, hopefully, they survive and are born normally (Table 3).[10]

LIMITATIONS OF TRANSGENIC ANIMALS

The following are the current limitations of transgenic animals for the production of pharmaceutical proteins:

- Transgenic animals are costly to produce, and they have high value. The cost of making one transgenic animal ranges from $20,000 to $300,000, and only a small portion of the attempts succeed in producing a transgenic animal.
- Problems exist with the method of producing transgenic animals such as random integration of the transgene into the genome. Many animals are born with gross birth defects (transgenic animals crated from such animals have no guarantee that these animals will be healthy, express the transgene in large amounts, or express the transgene in the right tissue.
- For new proteins, there is considerable cost and time in licensing, patent protection, and penetrating potential world markets.
- Most of the attractive proteins have been claimed already. Small organizations as well as established companies are studying the rest of the available proteins.
- The inadvertent release or escape of transgenic animals (particularly fish) into the wild where they could breed or compete with the natural population is often cited as a potential risk to the environment.
- Issues of public acceptance of GMO (Genatically Modified Organisms).
- Country-to-country variations in transgenic legislation.

TABLE 3

1. A human gene responsible for producing a desired protein
2. Isolation of the desired gene, which encodes the desired therapeutic protein
3. An animal is given hormonal treatment to produce a large number of embryos
4. Collection of embryos from the oviduct
5. Insertion of desired human gene into harvested ova (fertilized egg) via microinjection
6. Introduction of transgenic embryo to surrogate host (embryo transfer)
7. Development of offspring
8. Test to see if introduced gene is expressed or not (Gene product is manufactured)
9. Cloning of transgenic individuals to increase population rapidly

Common Strategy for Creation Transgenic Animal

COMMERCIALIZATION ISSUES[9]

Success in creating a transgenic animal that can produce the drug is far from guaranteed. About 10% to 30% of mouse embryos produce transgenic mice, but less than 5% of goats, sheep, or cows do. Production of the drug is measured during lactation after the animal is raised to maturity and bred. Because of the long time periods involved and low success rates, developing transgenic animals is currently very expensive (Table 4).

Although most protein drugs are made in milk, a notable exception is human hemoglobin that is being made in swine blood to provide a blood substitute for human transfusions. Because hemoglobin is naturally a blood protein, it is likely to be one of few exceptions to the usual method of production in milk. Furthermore, the economics of blood production are less favorable because to recover human hemoglobin, the animal producing it must be slaughtered.

Drugs currently made by or being developed in transgenic animals are listed in Table 4. Notice that pharming is expected to increase the value of animals significantly. In general, animal pharming is considered to be 5 to 10 times more economical on a continuing basis and 2 to 3 times less expensive in start-up costs than cell culture production methods.

ETHICAL ISSUES TO PHARMING

Many of the ethical issues that arise from pharming surround the treatment of animals.[11] Even with the 100% transgenic offspring produced by nuclear fusion, many are born with birth defects and gross abnormalities or do not produce the protein of interest. Additionally, while 100% of the animals born are transgenic, a large number of eggs are used in the process of finding one that can be implanted. This in itself may not be too alarming, however, most of the time the egg "donors" are slaughtered in the donation process.

Another issue is the idea of the age of the clones.[12] Dolly passed away at the age of 6 and a half. Considering that the average sheep lives for 11 to 12 years, this was quite young. Dolly died from a lung disease found only in old sheep, adding to speculation that cloning animals may effect their age. In fact, many cloned animals tend to die young, some within weeks of birth. When the Roslin Institute and PPL Therapeutics

TABLE 4

Drug	Drug Descriptions	Animal	Value/ Animal/Year($)
AAT	alpha-1-antitrypsin, inherited deficiency leads to emphysema	sheep	15,000
tPA	tissue plasminogen activator, treatment for blood clots	goat	75,000
Factor VIII	blood clotting factors, treatment for hemophilia	sheep	37,000
Factor IX		sheep	20,000
Hemoglobin	blood substitute for human transfusion	pig	3,000
Lactoferrin	infant formula additive	cow	20,000
CFTR	cystic fibrosis transmembrane conductance regulator, treatment of CF	sheep, mouse	75,000
Human Protein C	anticoagulant, treatment for blood clots	pig	1,000,000

Commercial Value of the Drugs Produced by Transgenic Animals

announced the birth of Molly and Polly, they had a litter of six lambs out of 14 cloned embryos. One died within hours of birth, and three more died shortly after, leaving the world with Molly and Polly.

Finally, as transgenic animals are being produced, biotech companies are quick to patent their work in order to maximize their profits. This raises the issue of animal rights, and whether or not these animals will be treated as sentient beings or whether they will simply be treated as walking factories.

CONCLUSION

The world market is growing for human pharmaceutical products. With current research being conducted, it is clear that within the near future, the medical field will see less-expensive protein therapeutics produced in a varity of non-conventional ways. Producing transgenic animals is still relatively expensive, however, costs are trending down, and transgenic animals have certain advantages over traditional laboratory methods for producing human proteins. More commercial uses of transgenic animals in food production is also likely. Apart from milk protein expression in egg, urine, or semen can be the attractive alternative. Reviewing existing policies and guidelines regarding transgenic animals is also necessary. New policies regarding transgenic and cloned animals may be necessary to ensure the safety and health of humans and animals. Ongoing public debate regarding transgenic technologies will ensure that further research and analyses will be demanded by animal producers, regulators, environmentalists, and the general public.

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BIOGRAPHIES

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IONTOPHORESIS

Hybresis™: The Hybridization of Traditional With Low-Voltage Iontophoresis

By: Thomas M. Parkinson, PhD; Margaret A. Szlek, MSc; and James D. Isaacson, MS

INTRODUCTION

Iontophoresis is a drug delivery technology that uses a low-level electrical current to enhance delivery of water-soluble ions across biological membranes, most commonly into or through skin.[1,2] The quantity and distribution of a drug delivered by iontophoresis depends on many system parameters, including the charge and molecular weight of the ion, the magnitude and duration of the electrical current, skin properties, drug patch, or electrode composition and drug formulation. An important attribute of this technology is the ability to precisely control drug delivery over time by controlling the electric current.

Recently, IOMED introduced the Hybresis™ Iontophoresis Drug Delivery System. The system consists of a miniaturized, wireless dose controller that connects directly to the integrated drug delivery patch. Although the Hybresis System was designed for the physical therapy market, its platform lends itself to applications in the pharmaceutical industry as a drug-device combination product.

CURRENTLY AVAILABLE TRANSDERMAL IONTOPHORESIS SYSTEMS

Standard Systems

IOMED pioneered commercial transdermal iontophoresis products over 30 years ago. Current IOMED iontophoresis products are sold predominantly in the physical therapy market and, based on marketing data, they are used most commonly for delivery of corticosteroids such as dexamethasone sodium phosphate to treat local tissue inflammation. These systems consist of a reusable battery-powered microprocessor DC current dose controller connected by wires to a disposable drug containment electrode placed on the treatment site and a disposable dispersive electrode placed nearby on the body. After the wires are connected between the dose controller and the two electrodes, the clinician sets the desired current level and iontophoretic dose. The iontophoretic dose represents the cumulative electrical charge over time (milliamperes [mA] X minutes [min] = mA-min) that directly determines the amount of drug delivered from the electrode patch. Typical settings for current and dose for these systems are 2 to 4 mA, and 40 to 80 mA-min, respectively. A major advantage of standard systems is their ability to maintain a constant current output and

FIGURE 1

adjust for variations in skin resistance among patients, skin sites, and over time. The iontophoretic dose is controlled, measured, and known by the clinician.

Integrated Systems (Patch-Only)

In the past few years, small, integrated systems containing a disposable low-voltage battery built into a single skin patch entered the physical therapy market. These systems avoid separate dose controllers and wires and are more convenient for clinicians and perhaps patients because in-clinic wear time is decreased or eliminated. However, the major disadvantage of integrated systems that use low-voltage batteries is that electrical current output from these devices will depend strongly on the skin resistance of the treatment site on individual patients. There is no feedback of the exact wear time required or the iontophoretic dose received within the prescribed wear time.

Hybresis System

IOMED developed and commercialized the Hybresis Iontophoresis Drug Delivery System, which combines the advantages of the aforementioned standard and integrated products while minimizing or eliminating their respective disadvantages.

Pharmaceutical Systems

Commercial systems mentioned above that target the physical therapy market should be differentiated, from other pharmaceutical drug-on-board iontophoresis products that are not addressed in this article. Vyteris has developed LidoSite® for delivery of the local anesthetic, lidocaine hydrochloride. ALZA (subsidiary of Johnson & Johnson) received NDA approval in May 2006 for IONSYS™ for the delivery of the opioid analgesic fentanyl hydrochloride.

TABLE 1

CATEGORY	HYBRESIS			6 V PATCH-ONLY		
	40 mA-min	60 mA-min	80 mA-min	40 mA-min	60 mA-min	80 mA-min
ELBOW (N=9 volunteers)						
Mean ±SD	0:34 ± 0:12	0:53 ± 0:18	1:12 ± 0:24	0:50 ± 0:23	1:11 ± 0:29	1:31 ± 0:35
Minimum	0:28	0:44	1:00	0:35	0:51	1:07
Maximum	1:08	1:43	2:17	1:53	2:29	3:03
Confidence Limits*						
∞ Lower	0:24	0:40	0:54	0:33	0:49	1:05
∞ Upper	0:44	1:08	1:32	1:09	1:34	1:59
KNEE (N=10 volunteers)						
Mean ±SD	0:50 ± 0:15	1:21 ± 0:21	1:51 ± 0:29	0:52 ± 0:31	2:37 ± 0:49	3:15 ± 1:00
Minimum	0:29	0:46	1:03	1:04	1:29	1:54
Maximum	1:16	1:57	2:36	3:11	5:11	6:31
Confidence Limits*						
∞ Lower	0:52	1:09	1:33	0:39	2:15	2:48
∞ Upper	1:00	1:35	2:09	2:07	2:59	3:42

* Based on the number of volunteer tested, there is a 95% confidence that the average of the wear times lie between Lower and Upper values.

Times (hr:min) to Achieve the Desired Total Charge (mA-min) With the Hybresis Mode (3 mA for 3 minutes + 6 V Patch) Versus 6 V Patch-Only: Data Summary & Descriptive Statistics.

FIGURE 2

Charging Station

BACKGROUND

Current - Drug Dose Dependency

In iontophoresis, an important relationship between electrical current, its time of application, and delivered dose of a drug is expressed by Faraday's law (D = I x T x MW/ |Z|xF). In which D is the amount of drug delivered in gram-equivalents, I is the current in Amps (Coulombs/sec), T is the time in seconds, MW is the molecular weight of the drug in gram/mole, Z is its valence, and F is Faraday's constant (96,500 Coulombs/mol). Assuming that all other parameters such as formulation and electrode compositions are kept constant, if

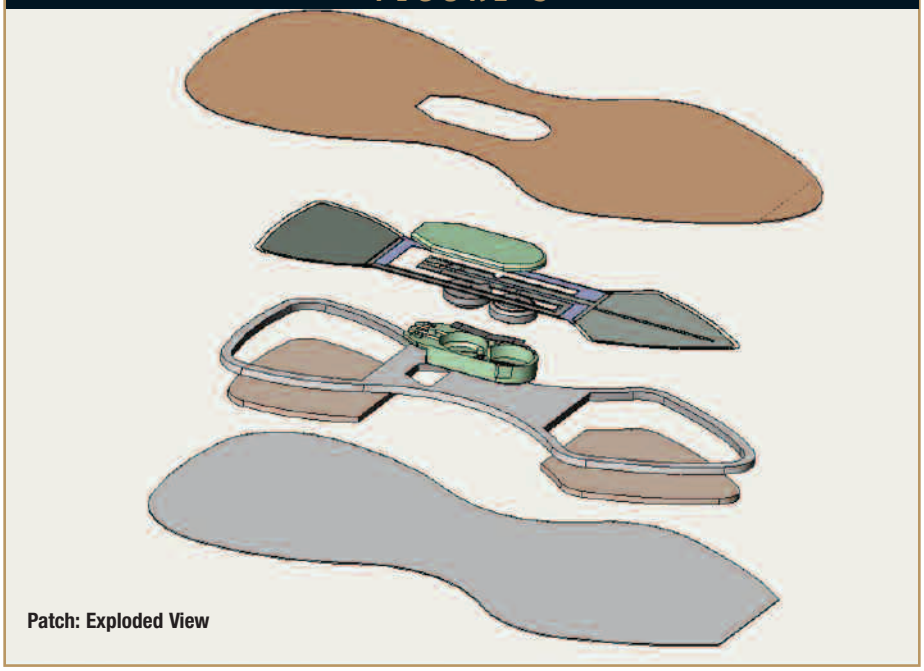
TABLE 2

Volunteer No.	ELBOW		KNEE	
	HYBRESIS	6 V PATCH-ONLY	HYBRESIS	6 V PATCH-ONLY
1, male	1:02	1:18	1:23	1:50
			1:32*	2:57
			**	2:06
			**	2:25
2, male	1:00	1:25	1:57	3:20
			2:04*	6:31
			2:33*	4:52
			2:05*	3:03
3, male	1:11	1:28	2:23	3:05
			**	3:11
4, male	1:07	1:22	2:16	2:34
			**	4:07
5, male	1:01	1:07	1:57	2:46
			**	2:55
6, male	1:09	1:30	1:28	3:06
			1:51*	3:16
			**	3:48
7, female	1:00	1:09	2:01	2:30
8, female	2:17	3:03	2:15	3:11
			2:36	4:00
			**	3:52
9, female	1:09	1:22	1:41	2:59
			1:19*	1:54
10, female	Data not collected		2:00	2:22

* Data generated with Skin Conductivity Enhancement treatments lower than 3 mA. These data are shown for illustration purposes only and are not included in the wear time statistics in Table 1.
** Data not available and/or deleted due to experimental set-up failure.

Times (hr:min) to Achieve 80 mA-min Dose for Each Study Participant With the Hybresis Mode Versus 6 V Patch-Only.

FIGURE 3



Patch: Exploded View

current or time is increased, the amount of drug delivered is increased.

Effects of Skin Resistance

Skin resistance is the most difficult system parameter to control. Electrical properties of the skin are unpredictable and have been shown to be changed by a variety of conditions, including hydration, pH, chemical additives, electrolyte concentration and valence, temperature, time of year, perspiration, skin disease, thyroid activity, and emotional state.[3] Skin resistance also varies from person to person and among body skin sites and can be changed by the passage of electrical current. The average initial skin resistance values reported in the literature varied between 20 k to 400 k , depending on the body site, and ranged between 4.5 k to 2,400 k among subjects.[4] Increased current or voltage can significantly decrease skin resistance within seconds to a relatively low resistance of approximately 7 ± 1 k regardless of the body site and individual.[4] This rapid skin resistance decrease is voltage-controlled with a threshold voltage required to accomplish these changes.[3] Decreased skin resistance often correlates with increased skin permeability, although the mechanism of this effect is not clearly understood.

From Ohm's law (I = V / R, in which I is the electrical current, V is the voltage, and R is the resistance), if current, which controls drug transport, is to remain constant, voltage must change to compensate for changes in skin resistance. Most standard commercial iontophoresis systems are constant current devices, where voltage output is sufficiently high to overcome an initial skin resistance and is regulated by the microcontroller to maintain current at a preset level.

In integrated iontophoretic systems

used in the physical therapy market, there is no current control, the battery voltage is too low to "compensate" for variable skin resistance, and there is no microprocessor to adjust the voltage to provide the constant current output. Because of this, it is impossible to determine the actual iontophoretic dose delivered over a specified treatment wear time for any given patient or body site.

HYBRESIS™ TRANSDERMAL IONTOPHORETIC DRUG DELIVERY SYSTEM

The Hybresis System contains a miniaturized rechargeable Controller that has typical features of the standard iontophoretic dose controller (IOMED Phoresor®) but connects directly to the Patch (Figure 1), eliminating all wires. The Controllers are charged in the Charging Station (Figure 2), which has four charging bays. The Patch has built-in batteries (Figure 3), which makes it possible to select between different treatment modes.

However, perhaps the most important innovation of the System is that it can provide a Hybresis (hybrid) mode consisting of a 3-minute Skin Conductivity Enhancement feature that is followed by the 6 V Patch-Only treatment. The Skin Conductivity Enhancement feature provides rapid decrease of skin resistance and normalizes or reduces its variability, thus making the Patch-Only wear time shorter and more predictable.

IOMED, Inc. has conducted studies in which iontophoretic current and voltage were measured in human volunteers under conditions representing the modes of operation of the Hybresis System. Results of these studies confirmed the expected effects on skin resistance and dosing times.

MATERIALS & METHODS

Transdermal Patches

Prototype integrated Hybresis drug and dispersive patches were fabricated at IOMED. Patches consisted of a breathable skin fixation tape with acrylic adhesive (3M Corporation), a non-woven fiber containment matrix (Lantor), and a silver ink anode (+) and silver/silver chloride ink cathode (-) to control pH during iontophoresis and to provide an automatic dose cut-off switch. The non-woven fiber matrix was impregnated with a polyethylene oxide thickening agent to ensure liquid retention by the matrix and uniform skin contact. Iontophoresis surface area of each matrix was approximately 9 cm^2. Both matrices were hydrated with 1.3 ml of physiological saline immediately prior to use.

Iontophoresis Power Supplies

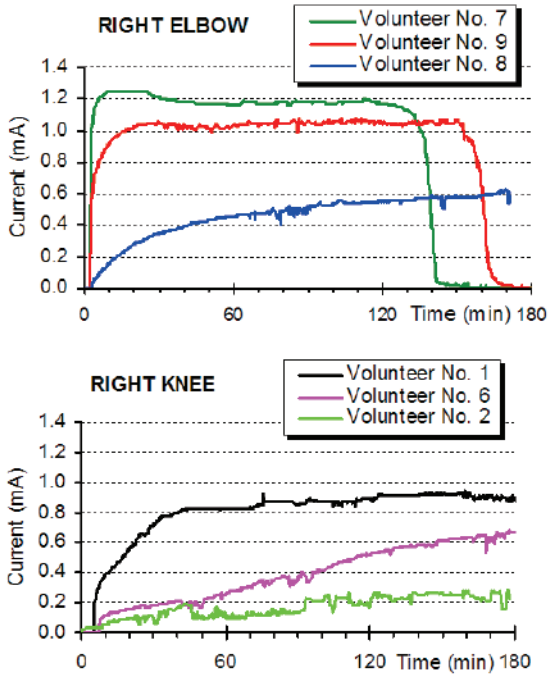
The Skin Conductivity Enhancement treatment with constant current iontophoresis was carried out at 3 mA for 3 minutes (8 mA-min) using the IOMED Multi-Schedule Data Logging Phoresor® (MS-DLP), hardware/software version Rev 1.0-1.0. [The actual iontophoretic dose is 8 mA-min rather than the calculated 9 mA-min because of the built-in current ramp-up and ramp-down required to reduce possible patient sensitivity and discomfort]. This research instrument is a programmable DC current generator, which measures and records current and voltage during iontophoresis.

Voltage-controlled iontophoresis during the integrated treatment phase was carried out using two 3 Volt button cell batteries (6 V total). Battery voltage and current output were measured at 15-second intervals using the IOMED miniature multi-channel Data Logging System (DLS). The DLS is a HOBO®-H08-006-04 four external channel data logger (Onset Computers, Inc.) integrated with an IOMED application-specific attenuation interface.

Test Methods

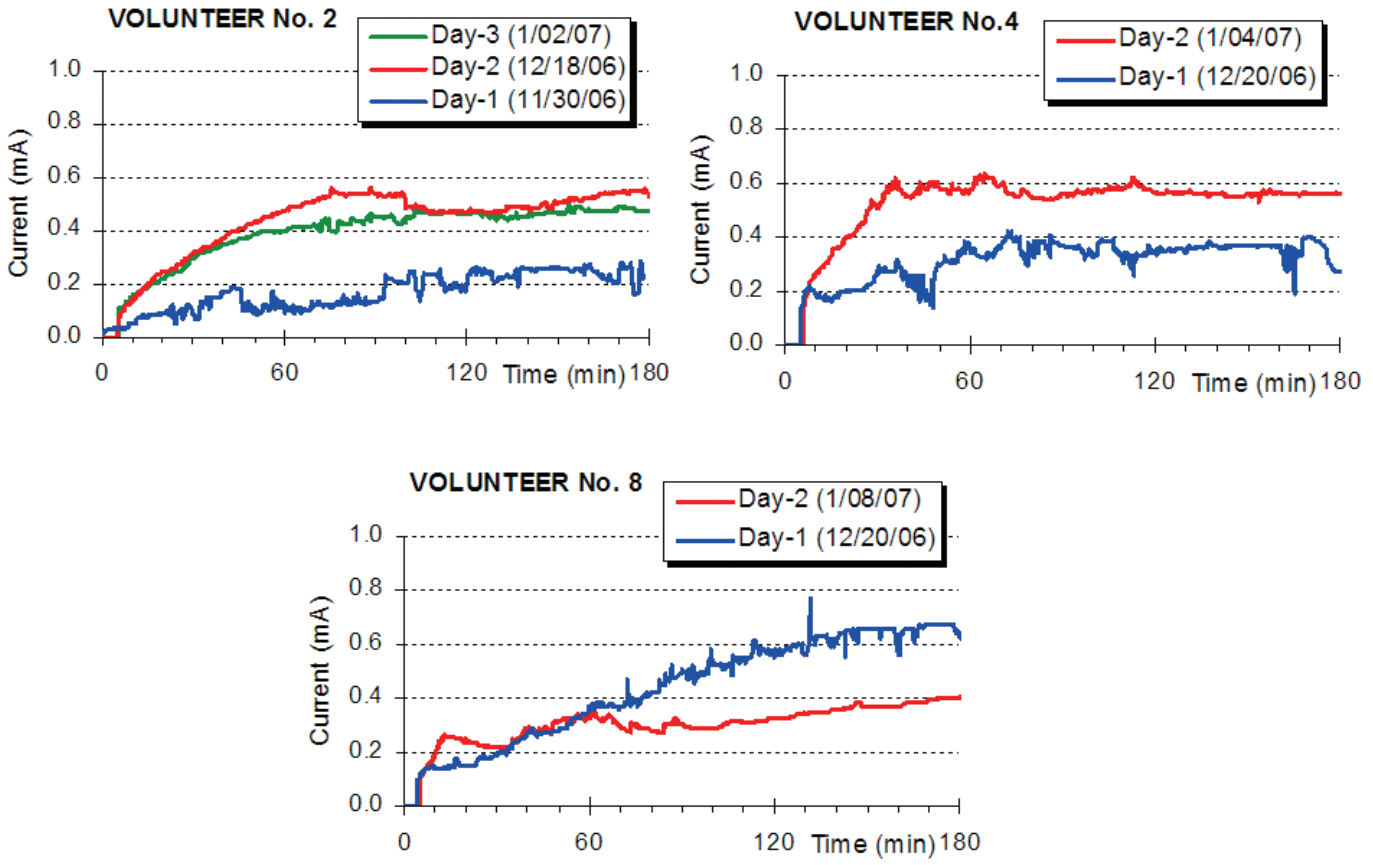
Six male and four female volunteers were tested on knees, and the same six male and three female volunteers were

FIGURE 4



Person-to-Person Skin Resistance Variability on Elbow and Knee During 6 V Patch-Only Dosing.

FIGURE 5



Day-to-Day Skin Resistance Variability on Knee During 6 V Patch-Only Dosing.

tested on elbows. As it was learned, these body sites represent areas of relatively high and low skin resistance, respectively. Sites were clipped free of hair, if necessary, and cleaned with an isopropyl alcohol pad prior to applying the patches. On the left side of the volunteers' bodies, a Skin Conductivity Enhancement treatment was provided using 3 mA of current for 3 minutes followed by a 6 V patch treatment. On the right side of the volunteers' bodies, a 6 V Patch-Only treatment was provided without the benefit of a Skin Conductivity Enhancement treatment. Cathodal (-) patches were placed over the lateral epicondyle or lower patellar tendon to simulate a common treatment of these sites with dexamethasone sodium phosphate, an anionic drug. Anodal (+) patches were placed approximately 1 inch away from the cathodal patches on the dorsal surface of the forearm and below the patella for the elbow and knee sites, respectively. Right and left sites were tested simultaneously; elbows and knees were tested on separate days.

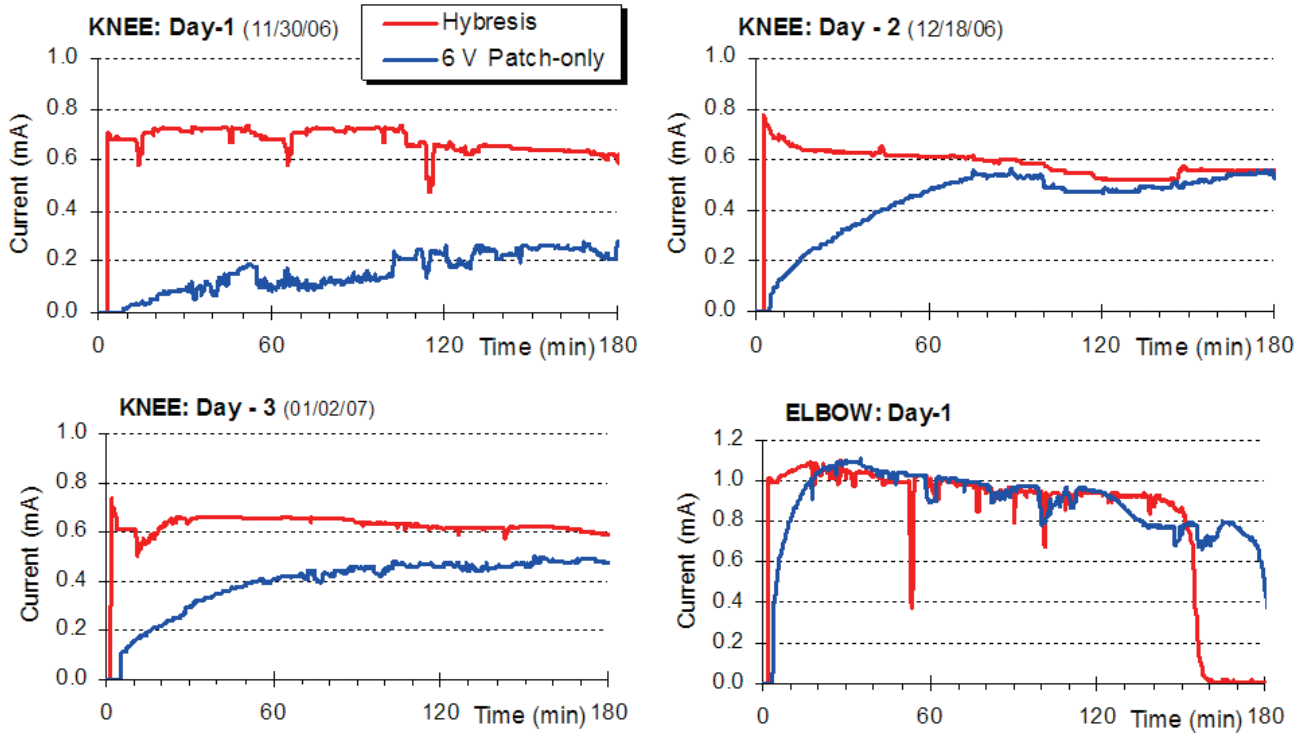
RESULTS

Table 1 summarizes results of the times required to deliver 40 mA-min, 60 mA-min, and 80 mA-min iontophoretic doses with 3 mA for 3 minutes Skin Conductivity Enhancement followed by 6 V treatment and with 6 V Patch-Only simulated treatment. Table 2 shows times required to deliver an 80 mA-min iontophoretic dose for each volunteer with both treatment modes. The following conclusions can be drawn from these data.

6 V Patch-Only

For the 6 V Patch-Only (integrated treatment), there are considerable differences in times required to deliver 80 mA-min among all volunteers and for the same volunteer tested over 1 to 4 days (see, for example, volunteers No. 2 and No. 8 in Table 2), and between the elbow and knee skin sites (see, for example, volunteer No. 2).

FIGURE 6



Effect of Skin Conductivity Enhancement (Hybresis Mode) on the Current Output: Volunteer No. 2.

Skin Conductivity Enhancement

Skin Conductivity Enhancement (Hybresis mode) significantly decreases the time required to achieve an 80 mA-min dose in relatively high-resistance patellar skin, but has less effect in relatively low-resistance epicondyle skin. Because it is difficult, if not impossible, to predict relative skin resistance of treatment sites in individual patients, Skin Conductivity Enhancement provides a means of normalizing or reducing the variability of skin resistance when needed. This allows the clinician to achieve the desired total iontophoretic dose within a recommended treatment wear time with greater certainty.

Figure 4 shows current output for a 6 V Patch-Only over 3-hour treatment period on knees and elbows in 6 test volunteers. Note that the current output is directly related to the skin resistance; the higher skin resistance the lower the current. Figure 5 shows the day-to-day variability of current output with the same treatment in three volunteers. These results clearly show the wide variability in skin resistance, which would be encountered in a typical patient population undergoing iontophoresis therapy. Figure 6 shows Skin Conductivity Enhancement effects on the knee of one volunteer treated three times and the lack of effect on the elbow. Note the relatively constant current output achieved with the Hybresis mode (red lines) despite the difference in the day-to-day skin resistance as evidenced by the electrical current output (blue lines). Similar results to those shown in Figures 4 to 6 were seen with all test volunteers.

Standard Iontophoresis

The Standard mode of the Hybresis System provides 40 mA-min treatments at 2 mA, 3 mA, or 4 mA. Treatments at these current levels take 20, 13, and 10 minutes, respectively, and are terminated automatically when the 40 mA-min dose is reached.

SUMMARY

The Hybresis Transdermal Iontophoretic Drug Delivery System is capable of administering Standard, Patch-Only, or Hybresis modes of treatment. Standard treatments are carried out with the reusable Hybresis Controller attached to the Patch and is intended to be carried out in a clinical setting over a 10- to 20-minute period. Patch-Only treatments are carried

out using only the Patch, allowing the patient to leave the clinic after application to receive treatment over the next few hours. The innovative Hybresis mode is carried out with the Hybresis Controller attached to the Patch for a 3-minute Skin Conductivity Enhancement period in the clinic. The controller is then removed, and the remainder of the treatment is carried out with just the Patch as the patient goes about his or her normal activities for the next 1 to 2 hours, depending on the prescribed dose of 40 mA-min, 60 mA-min, or 80 mA-min. The versatile Hybresis System provides controlled drug delivery with the convenience and time-savings of a patch.

The Hybresis System was designed predominantly for use in the physical therapy market. However, its miniaturized, wireless dose controller directly connected to the integrated transdermal patch lends itself to development of drug-specific iontophoresis delivery systems for the pharmaceutical industry.

ACKNOWLEDGEMENT

The authors wish to thank IOMED's Chief Mechanical and Electronic Design Engineers Jon Beck and Robert Hause, respectively, for their innovative ideas and countless hours dedicated to this project. Without their contributions, the Hybresis System never would have come to fruition.

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BIOGRAPHIES

Dr. Thomas M. Parkinson has over 40 years experience in the pharmaceutical and medical device industries in product development, R&D management, clinical and regulatory affairs, and business development. Dr. Parkinson was Vice President of R&D and General Manager at Iomed and currently is a Research and Business Development consultant to Iomed. Prior to joining Iomed, he was Vice President of R&D at Sequus, Inc., where he was responsible for biopharmaceutics, clinical testing, and developing regulatory strategy for new liposome drug delivery systems. Dr. Parkinson served as Director of Medical Affairs for Collagen Corporation, and Director of Biological Research at Dynapol, Inc., a chemical technology company. He was also head of the Atherosclerosis Research Section of The Upjohn Company, where he developed Colestid®, Upjohn's first cholesterol-lowering drug. Dr. Parkinson earned his BS in Chemistry from Providence Collage and his PhD in Biochemistry and Medical Sciences from the University of Florida College of Medicine.

Ms. Margaret Szlek joined Iomed's R&D group in 1990. Since joining the company, she has held positions of increasing responsibility, and currently serves as Manager of Feasibility and Biologic Testing. In this role, Ms. Szlek has lead Iomed's preclinical and biologic testing programs for the development of the transdermal iontophoresis products, including the OcuPhor® Ocular Iontophoresis Drug Delivery System. Ms. Szlek has extensive experience in the development of *in vitro* and *in vivo* drug transport, pharmacokinetic, and toxicology studies that support development of the iontophoretic drug delivery systems. Ms. Szlek earned her MSc in Biology from the University of Maria Sklodowska-Curie in Poland.

Mr. James D. Isaacson has served as Iomed's Director of Design and Development since joining the company in 2004. Mr. Isaacson has over 21 years of experience as a product design engineer, with over 18 years focused specifically on medical devices. He has relevant experience managing engineers in a product development capacity, and has a strong background in project management and design controls. Prior to joining Iomed, Mr. Isaacson spent 9 years at Megadyne Medical Products, Inc., and previously was with Cardiopulmonics, Inc., Cobe Laboratories, Inc., and Diconix, Inc., a subsidiary of Eastman Kodak. Mr. Isaacson earned his MS in Mechanical Engineering from Massachusetts Institute of Technology and his BS in Mechanical Engineering from the University of Michigan.

SPECIAL FEATURE

The State of Systemic Pulmonary Delivery: One Year After Exubera's Approval

By: Cindy H. Dubin

INTRODUCTION

Touted as the first-generation product of its kind, Pfizer's Exubera has done exactly what industry insiders hoped it would — open doors and conversations about how to improve systemic pulmonary delivery devices. Now, the products coming behind Exubera are bound to be significantly improved. Exubera, the first inhalable insulin, will soon arrive on most pharmacy shelves. Pfizer and some industry analysts believe inhaled insulin — delivered through a small pump about the size of a flashlight and filled with dry powdered insulin packages — will be quickly adopted by some of the nation's 14.6 million diagnosed diabetics and could account for up to $2 billion a year in sales. That would make it a blockbuster drug at a time when the pharmaceutical industry is having a hard time finding new medications.

"Exubera was a great step forward for the industry," says Igor Gonda, PhD, President and CEO of Aradigm Corp. "So many of us don't understand why Exubera has not been made into as big an instant success as expected."

"Expectations are high for Exubera, and it can be difficult to meet them," warns Anthony Garramone, Vice President and General Manager of Baxter Healthcare, Inc.'s subsidiary Epic Therapeutics, Inc.

Although Pfizer stands behind its predictions for early sales, there's evidence of mounting resistance among doctors and some patients to the new diabetes drug. One hurdle is the price. The pump and insulin packets cost about $2,100 a year.

Another obstacle, some doctors are concerned that inhaled insulin causes slight declines in air capacity in the lungs. Those findings led the FDA to require Pfizer to conduct additional research that isn't expected to be completed for several years.

Mr. Garramone likens Exubera to early cell phone development. "The first-generation products were bulky, costly, not portable, and did not offer good reception. But there was promise of improvement. Exubera is a first-generation pulmonary insulin delivery system whose size and maintenance and training requirements can make it difficult to use properly. But it is a great first-generation product and has to be thought of in that way."

"The approval of Exubera has encouraged the pulmonary drug delivery community in the expectations for further systemic delivery applications of pulmonary devices," says Troels Keldmann, PhD, Managing Director, Direct-Haler A/S. "Also, as inhaled insulin now is proven, the search has begun to find how simple and convenient an inhaled insulin delivery system can become."

ALKERMES PARTNERS TO EXPAND COMMERCIAL POTENTIAL OF PULMONARY PLATFORM

Alkermes' proprietary AIR® technology provides a platform for developing medications with the potential to improve outcomes by allowing patients to consistently inhale

FIGURE 1

Alkermes & Eli Lilly are Developing the AIR Insulin System, Which Uses a Small, Breath-Activated Inhaler

their medication, an alternative to frequent injections. The science underlying the AIR technology enables the formulation of drugs into large, dry particles with low mass density. As a result, these powders can be readily inhaled to the deep lung using a small, easy-to-use, breath-activated inhaler.

"Alkermes is unique as we emphasize the engineering of innovative drug particles, which significantly simplify the mechanics of the inhalation device," says Jen Schmitke, Director, Product Development, Alkermes.

Part of Alkermes' business strategy is to develop products both on its own and with partners. Alkermes has two proprietary technology platforms (extended-release injectable and pulmonary) that offer unique opportunities to develop medications that can improve patient outcomes. According to Ms. Schmitke, partnerships offer the following important benefits:

- Partnerships enable us to accelerate clinical development, access commercial capabilities and knowledge, and bring important expertise and financial resources.
- Partnerships provide access to unique molecules with established safety and efficacy profiles, such as trospium chloride and parathyroid hormone.
- With its partners, Alkermes can pursue more products across a broader range of therapeutic areas while simultaneously accelerating the advancement of products to approval.

Eli Lilly and Alkermes are developing the AIR Insulin System (Figure 1) for the treatment of type 1 and type 2 diabetes. The system is currently in Phase III development. It is expected that a new drug application for the AIR Insulin System will be filed with the FDA in 2009.

"The AIR Insulin System uses a small, breath-activated inhaler that fits in the palm of the patient's hand, which we believe will offer convenience and ease of use for patients," says Ms. Schmitke.

Lilly and Alkermes are also developing AIR PTH, an inhaled formulation of parathyroid hormone, for the treatment of osteoporosis. AIR PTH builds on the profile of Lilly's recombinant PTH, FORTEO® for the treatment of osteoporosis (teriparatide (rDNA origin) injection). AIR PTH is currently in preclinical development. Alkermes and Lilly expect to begin a Phase I study of AIR PTH in the first half of calendar 2007.

Alkermes and Indevus Pharmaceuticals, Inc. are developing ALKS 27, an inhaled formulation of tropsium chloride, for the treatment of chronic obstructive pulmonary disease (COPD). The goal is to develop a once-daily, inhaled medication for the treatment of COPD, the fourth largest cause of death in the US. Phase I clinical development has been completed. Alkermes and Indevus expect to begin a Phase IIa study in the first half of calendar 2007 designed to evaluate the clinical efficacy of ALKS 27 in patients with COPD. ALKS 27 builds on the established safety profile and efficacy of trospium chloride, the active ingredient in SANCTURA®, Indevus' drug currently marketed for overactive bladder.

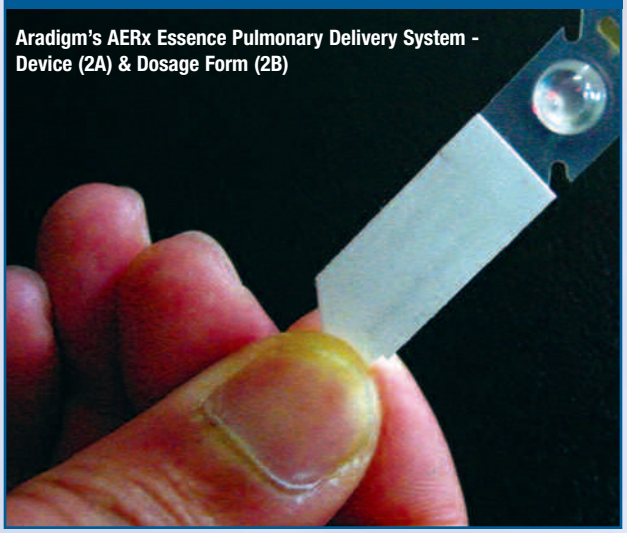
Alkermes and its partners have not publicly announced expected launch dates for any of these product candidates.

ARADIGM FOCUSES ON PULMONARY DELIVERY & TREATMENT OF SEVERE RESPIRATORY DISEASE

This past year, Aradigm defined itself as strictly a pulmonary company, selling its Intraject sumatriptan injection system to Zogenix. In July 2006, the company also obtained non-dilutive

FIGURE 2A

FIGURE 2B



Aradigm's AERx Essence Pulmonary Delivery System - Device (2A) & Dosage Form (2B)

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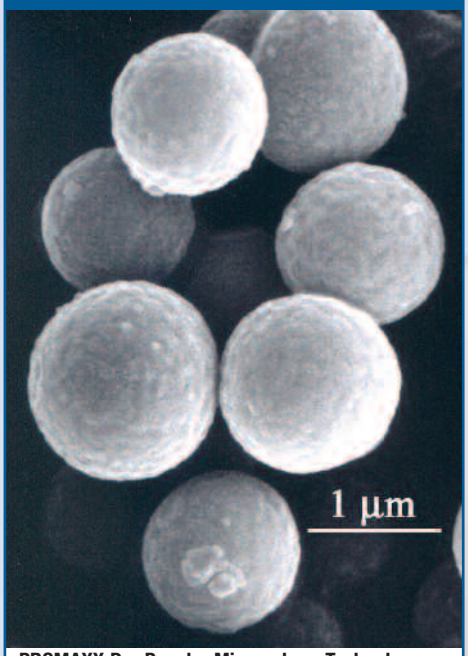
FIGURE 3



PROMAXX Dry Powder Microsphere Technology Enables the Creation of Uniformly Sized Microspheres That can be Tailored to Formulate Many Types of Drugs for Pulmonary Delivery

financing of $27.5 million from Novo Nordisk, its partner for inhaled insulin. Since then, the company, under leadership of Igor Gonda, PhD, has also raised $33 million from new investors.

"We are focusing on developing inhaled products for severe pulmonary disease," says Dr. Gonda. "This is moving us toward a Specialty Pharma model, having a core in severe pulmonary disease and a dedicated sales force."

Aradigm combines its AERx pulmonary delivery platform with formulations to create products that enable better health outcomes and quality of life for patients. The AERx platform, designed for inhaled delivery to and through the lung, is in late-stage clinical development. The central element of the system is the AERx Strip dosage form, which contains liquid formulations and a disposable nozzle to ensure aerosol performance (Figures 2A and 2B). The nozzle's design can be adjusted for various formulation characteristics and treatment requirements to regulate the particle size and the primary deposition area of the therapy.

AERx hand-held devices utilize a small piston mechanism to expel the liquid formulation from the AERx Strip. The first-generation AERx technology is being developed for the delivery of inhaled insulin. According to Dr. Gonda, Aradigm's AERx insulin Diabetes Management System (iDMS), which has been licensed to Novo Nordisk for development and commercialization in return for royalties, is in Phase III testing for type 1 and type 2 diabetes. Because the formulation is a liquid, the patient can dial the number of insulin units that are delivered. The device also guides the patient into the correct breathing pattern in every inhalation. The product is expected to hit the market in 2010.

A new-generationl device, the AERx Essence™, is designed primarily for topical lung delivery of proteins and small molecules and systemic delivery of small molecules.

Aradigm also has liposomal technology for slow-release pulmonary formulations. It has received orphan drug designation from the FDA for an inhaled liposomal formulation of ciprofloxacin for the management of bronchiectasis (BE) and cystic fibrosis (CF). The liposomal ciprofloxacin is an aerosolized formulation of this anti-infective drug that was designed to prolong its anti-infective properties in the lung in order to treat the related infections found in BE and CF patients, while minimizing the concentration of the drug in the rest of the body.

BAXTER'S PROMAXX IN PHASE I CLINICAL STUDIES

PROMAXX dry powder microsphere technology enables the creation of uniformly sized microspheres that can be tailored to formulate many types of drugs for pulmonary delivery (Figure 3). The initial Phase I study demonstrated the potential for the technology using insulin, and PROMAXX inhaled insulin is now in a follow-up Phase I study.

"In the first study we conducted for human pulmonary delivery, we got great scintigraphy data," says Vice President and General Manager Anthony Garramone. "Our second study is focused on pharmacokinetic and pharmacodynamic data."

What makes PROMAXX unique is that the simple, essentially excipient-free powder can be used with an off-the-shelf inhaler, one not specifically developed for PROMAXX.

"We've always known the powder had great aerodynamic characteristics," explained Mr. Garramone. "We don't need to formulate the microspheres with anything but insulin, and that is a key differentiator in this market."

While insulin delivery is the lead program, there are other opportunities for PROMAXX. The company is looking to team up PROMAXX with other types of molecules, for example nucleic acids, for pulmonary delivery. The company's plan is to demonstrate how good this technology is. Baxter is taking steps to commercialize PROMAXX. Once the current studies are complete, the company will seek a marketing and development partner. Mr. Garramone expects that the first pulmonary applications of the PROMAXX technology will be commercialized in 2013.

DIRECTHALER™ HAS WORLDWIDE APPEAL

The DirectHaler Pulmonary device is for dry powder intrapulmonary delivery. Each premetered, prefilled pulmonary dose has its own DirectHaler pulmonary device (Figure 4). The device is hygienically disposable and is made of 0.6 grams of polypropylene. The compact and portable device has proven performance in clinical trials and proven acceptability in the US, Europe, and India. The device platform holds potential for customizations for any inhaled delivery application.

"The DirectHaler device was originally developed in response to the need for devices that are easy to use, easy to instruct, and easy to check, all to achieve improved patient compliance and limit the time spent on instructions from healthcare professionals," says Troels Keldmann, PhD, Managing Director.

"DirectHaler has successfully completed clinical trials (Phase I, II, and

III) with a range of generic asthma compounds and is matured and available for licensing and development. As the device is registered with the active substance, as one system, then the time to market depends on our licensees' choice of active substance to take to market in the DirectHaler," explains Dr. Keldmann.

The DirectHaler is suitable for therapies with dosing regimens, such as once-daily dosing (eg, asthma, COPD), once-a-few-times dosing (eg, respiratory infections, pain management), and once-only dosing (eg, vaccines).

"Further, we have two new pulmonary devices in an advanced prototype stage. These are aimed at more demanding pulmonary delivery tasks; high drug payloads and deeper lung delivery."

The DirectHaler and the two new device prototypes address all the existing application areas for pulmonary delivery (eg, asthma, COPD, respiratory infections) but also the emerging and future applications involving systemic delivery.

3M LEVERAGES MDIs FOR MACROMOLECULES

With more than 50 years' experience, 3M Drug Delivery Systems continues to work at improving the performance of the MDI in many areas.

FIGURE 5

3M Drug Delivery Systems Continues to Work at Improving the Performance of the MDI in Many Areas

This includes developing valves to address product robustness in the hands of patients, improved dose content uniformity, and elimination of the need for priming.

To improve the ability to develop suspension formulations with excellent dose reproducibility and enhanced lung deposition, novel particle technologies are being developed and utilized at 3M. These novel particle technologies have the potential to markedly improve suspension of MDI delivery. Advantages include the ability to formulate drugs that otherwise could not be delivered to the lungs and the potential for sustained-release delivery.

"We are also working with partners to develop proprietary excipients and have gathered excellent results, including human clinical exposure," says Dave W. Schultz, Research Specialist at 3M. "These excipients have demonstrated benefits as both solubilizers and suspending aids with multiple drugs."

In addition, 3M is increasing its offerings of other hardware components, including a variety of canister and actuator technologies. 3M has developed a dose counter, which will address the industry's need for a true dose counter, explains Dr. Schultz. This is a robust design, fully integrated into the actuator. Formulations can be improved with conventional or novel excipients to improve suspension characteristics or dissolve drugs to create solution formulations.

Currently, 3M is focused on MDIs for asthma (Figure 5). However, exploratory data has demonstrated the feasibility of leveraging the MDI technology platform for systemic delivery, including macromolecules. Investigations, including particle size reduction techniques, stability in CFC-free propellant systems, delivery performance studies, and protein compatibility with container closure systems, have shown promising results. Work in the area of particle size reduction has resulted in a stable process for obtaining protein particles in the respirable range.

FIGURE 4

The DirectHaler Pulmonary Device is for Dry Powder Intrapulmonary Delivery

"We have completed a feasibility program on a model protein using our particle engineering technology to reduce the particle size. The formulations showed excellent performance and stability," says Dr. Schultz.

The work at 3M along with the approval of Exubera confirmed that pulmonary delivery of biopharmaceuticals is possible.

"The increase in confidence has made companies aggressively pursue development opportunities of biopharmaceuticals in a number of different delivery devices, including MDIs," continues Dr. Schultz. "These developments demonstrate that the 50-year history of the MDI can successfully be leveraged against 21st-century technologies to broaden future platforms that meet the needs of systemic delivery. We expect to see further advancements, acceptance and ultimately, more approvals in this segment."

VECTURA DPIs COULD REACH MARKET IN 4 YEARS

Vectura has a range of dry powder inhaler (DPI) devices and formulation technologies designed to address specific market needs and enable the development of products with challenging performance requirements

FIGURE 6

Aspirair & GyroHaler

Vectura GyroHaler & Aspirair Dry Powder Inhaler Devices

Aspirair GyroHaler

FIGURE 7

Ventaira's Commercial Device (Photo Courtesy of RKSPhotography.com)

for both local respiratory therapies and for delivery of drugs through the lung for systemic applications.

GyroHaler® is a multi-unit dose DPI device designed to deliver locally acting drugs to the lung. It is compact and easy to use with a small number of molded parts in order to allow short device development times and competitive manufacturing costs. The device contains up to 60 doses and is disposable after use. It is designed to have competitive aerosolization characteristics and to provide excellent protection from moisture and light using sealed foil blisters. Certain core GyroHaler technology has also been non-exclusively licensed to Boehringer Ingelheim, which is developing its own branded form of the device for its products.

Aspirair® is an "active" inhaler technology. This breath-activated device is designed primarily to allow delivery with high lung penetration and low variability, essential for drugs that are intended for systemic delivery.

Clickhaler® is a multi-dose, reservoir DPI approved for use and marketed to treat asthma and COPD with a variety of drugs in a number of European countries and Japan (salbutamol, beclometasone, formoterol, budesonide, and procaterol).

Duohaler® is a fixed-combination therapy, multi-dose DPI. It has two separate reservoirs that feed two separate formulations into separate metering chambers from which the drugs are delivered to the patient in the same breath. Duohaler is in the industrialization validation phase of development and is expected to enter clinical trials in 2007. Duohaler is suited for the delivery of certain fixed combination therapies for asthma and COPD.

S2 Unit Dose is a re-useable or disposable single-dose DPI at an early stage of development, which has the potential to deliver a range of therapeutics in high concentrations. Its dispersion mechanism means that minimal patient effort is required to ensure drug delivery to the patients' lungs.

PowderHale® is Vectura's patented dry powder formulation technology designed to allow aerosolized drug particles to achieve high lung penetration with low dose variability. This is achieved by the incorporation of an additional pharmacologically inactive excipient, known as a Force Control Agent (FCA), to the active drug component or the carrier-based formulation. Examples of patent-protected FCAs include magnesium stearate and L-leucine. PowderHale technology provides the capability to deliver a consistent fine particle dose of drug, closer to the nominal delivered dose. This is achieved by modification of the interactive forces holding together the active drug particles and the carrier particles. In this way, benefits can be achieved in deaggregation and aerosolization, as well as in bulk powder handling and metering of the formulation. Vectura has an agreement with GSK concerning the use of PowderHale formulations for GSK products.

The GyroHaler and Aspirair inhaler devices (Figure 6) are in advanced commercial development and are used in a number of Vectura's own pipeline product programs as well as being developed and evaluated in conjunction with Vectura's product partners and device licensees. These devices are likely to reach the market over the next 4 to 5 years.

Clickhaler is in commercial manufacture and approved for use in several countries for several respiratory treatments. The Duohaler extension of the Clickhaler technology is in advanced development and is expected to reach the market in the next 3 to 4 years. The S2 single-unit DPI is at the functional prototype stage and could enable fast-track development.

In January 2007, Vectura acquired Innovata, a UK company also with an international reputation for its inhalation technologies and development capabilities.

VENTAIRA PROVES BREADTH OF MYSTIC™

In the past year, Ventaira has made progress in advancing from a research platform to a commercial product (Figure 7). The company has completed development of its commercial device, which utilizes its Mystic technology, and signed a manufacturing agreement

with Nypro, a medical device manufacturer. Nypro has already manufactured Ventaira's clinical devices and is now proceeding with manufacturing its commercial devices in this month.

In addition, the company has completed a scintigraphy/PK study that demonstrated rapid absorption, high bioavailability, and reproducibility.

"The lung deposition performance of our technology in human subjects is superior to any device on the market today," says Leslie Williams, President and CEO.

The clinical performance has remained consistent throughout the past 6 years as Ventaira has reduced the device to practice.

"Additionally, we have advanced our formulation capabilities and successfully aerosolized a range of compounds, small molecules, as well as peptides," says Ms. Williams. "We have advanced our formulations in a portfolio of pain products, such as fentanyl for breakthrough pain as well as cannabinoids. These products are on stability, and we have initiated preclinical toxicology work on fentanyl."

Ventaira has successfully aerosolized a portfolio of compounds using its Mystic technology. These compounds represent a range of chemical classes of drugs and therapeutic areas, including asthma, COPD, diabetes, pain, multiple sclerosis, osteoporosis, anti-infectives, and immunosuppressives.

The past year also saw a shift in Ventaira's internal development focus from topical treatment of asthma and respiratory disease to systemic treatments.

"This not only demonstrates the breadth of the technology but also allow us to capitalize on a rapidly growing inhalation market in a variety of therapeutic areas using the lung as a portal for drug delivery," says Ms. Williams. "Keep in mind that although we have shifted our internal focus to systemic treatments rather than respiratory diseases, Ventaira's Mystic inhaler remains well suited to deliver drug to the lung to treat respiratory diseases as well."

AN INDUSTRY WITH SOME GROWING TO DO

The pulmonary delivery market has evolved and will continue to do so throughout the next decade, according to industry insiders. Some estimate that if an inhaler can prove that it can deliver drug deep into the lung and deliver systemic drugs, the market for such an inhaler could reach $25 billion a year. It is clearly a growing field that will continue to expand as time goes on.

Jen Schmitke, Director, Product Development, Alkermes, says "We are encouraged there is a pulmonary delivery system on the market today and that there is a clear regulatory pathway by which one can attain approval of a novel pulmonary delivery product. For a major disease like diabetes that is increasing significantly, it is important that new treatment options become available."

But let's not get ahead of ourselves. This is an industry with some growing to do. "Although Exubera represents a major milestone in using the lung as a portal for drug delivery, it is clear this field is in its infancy and that various device platforms will have different advantages," says Ms. Williams. "There are many opportunities for the pulmonary drug delivery space, and it is a very exciting time for those of us in the space."

Doug Smalley, Director of Business Development, Vectura, says "The long-awaited approvals of Exubera in the US and Europe have provided a boost to the pulmonary delivery market by confirming the confidence many companies are placing in the benefits of this route and in new technologies for the delivery of products for systemic delivery. In the area of insulin alone there are several clinical-stage inhaled programs underway. It has also has confirmed the lung as a fast non-invasive drug portal that is well accepted by patients."

The sector will grow by increased investment in the range and number of new product concepts using inhalation technology starting in development and successfully completing approval. The challenges are manifold, but companies like those mentioned in this article (with the right technologies and capabilities) will increasingly address and resolve the issues and most certainly achieve commercial success. ◆

BIOGRAPHY

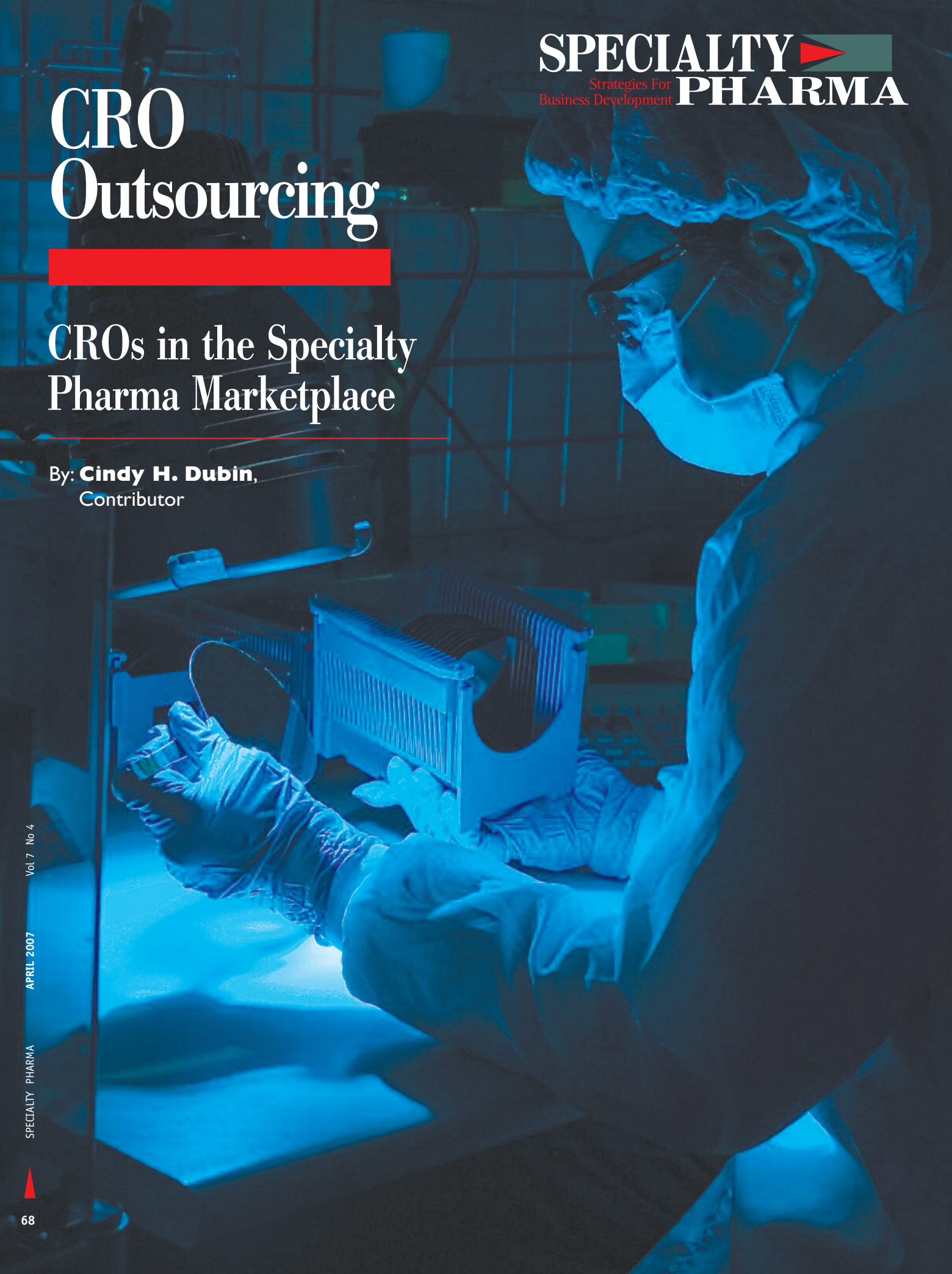
Ms. Cindy H. Dubin has been a professional journalist since 1988. She is currently a Contributing Editor to Drug Delivery Technology as well as Editor of its Specialty Pharma section. Prior to these positions, she spent several years focusing her writing on pharmaceutical formulation and development. She has been recognized by the American Society of Business Press Editors for an article she wrote on nanotechnology, and her writing has been awarded by the prestigious Neal Award Committee for Journalistic Excellence. Ms. Dubin earned her BA in Journalism from Temple University in Philadelphia and her certificate in Business Logistics from Pennsylvania State University.

SPECIALTY PHARMA
Strategies For Business Development

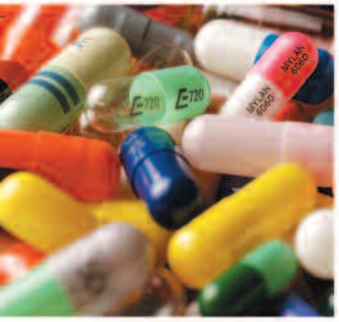
CRO Outsourcing

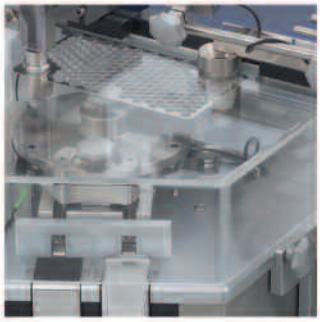
CROs in the Specialty Pharma Marketplace

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



Need to reduce the time-to-market for your latest drug?





Utilize capsules.

Pharmaceutical companies are taking months off the first-in-man timeline by micro-dosing API directly into capsules. But that's only one way capsules help gain time in the race to market. Capsule formulations require fewer processing steps, meaning less time for process optimization, documentation and equipment validation. And when early-phase clinical trials are conducted in capsules, there is no need for the time-consuming bioequivalence testing that would be needed to develop the commercial dose in a tablet. Finally, capsule formulations require fewer excipients than tablets, resulting in less time to select, evaluate, and validate raw materials.

This time saved during development translates directly into more selling time under patent protection, making the capsule dosage form decision not only simple, but smart.

For more information, visit **www.capsugel.com**

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Introduction

Outsourcing to CROs by pharmaceutical and biotechnology companies continues to be a growing trend with more than 20% of cardiovascular and oncology clinical development currently being outsourced, according to market research analysts at Frost & Sullivan. Additionally, therapeutic areas, such as metabolic diseases, are likely to be increasingly outsourced in the next 12 to 24 months.

Due to increased globalization of clinical trial activity, there is indication of a possible slight shift in clinical trial activities from North America to other regions. North America's share of clinical trials is expected to decrease from 61% to 53% in the next 3 to 5 years, indicates Frost & Sullivan.

The primary reasons for outsourcing include a reduction in manpower required by pharmaceutical and biotech firms, greater geographic coverage provided by CROs, better access to patients for clinical trials, and an enabling of R&D in non-core therapeutic areas.

Specialty Pharma asked some of the industry's leading CROs to address these and other issues, particularly how they are working within the Specialty Pharma framework and how those partnerships can become a success.

Q: What should a Specialty Pharma company expect its CRO to be able to deliver?

Dr. Mark A. Goldberg: The landscape of the pharmaceutical industry is evolving as Specialty Pharmaceutical companies play an increasingly important role in delivering innovative and vital compounds. When working with a service provider, Specialty Pharmaceutical companies should expect a true partnership and work with a service provider that has a sense of ownership and accountability for their program. For many Specialty Pharmas, success may hinge on just one compound. Therefore, the service provider must play a proactive role and work not only to identify problems but also to be strategically focused and offer innovative solutions. Specialty Pharmaceutical companies should also expect their service provider to have a broad range of therapeutic area expertise, extensive global capabilities and reach, and a comprehensive technology offering to be able to design the most cost effective and efficient clinical development program possible.

Dr. John Hubbard: Because the focus of Specialty Pharma tends to be in product optimization, either through changes in formulation or delivery technology, it is important that the CRO understands the clinical, therapeutic, and commercial strategy. This will enable the CRO to provide the necessary regulatory and clinical development expertise for protocol development, development strategy, and study execution plan. SP companies need to select a CRO that can provide comprehensive services from Phase I through Phase IV and Peri-approval services. Moreover, strong therapeutic and operational knowledge applied to developing a feasible study protocol is also an important strategic service that a CRO can provide.

Mr. Jeff Thomis: Any customer should expect consistent delivery of high-quality services, whether in the form of regulatory consulting, patient recruitment, delivery of clean data on time, or post-marketing safety surveillance. A CRO should also help the customer recognize the ultimate goal – whether that is an approved product label or a more highly valued product pipeline – and help the customer develop a plan to achieve that goal. A good CRO is more than "arms and legs;" it has the experience and expertise to work with an SP company to successfully navigate the regulatory maze. An SP company should look for synergies with the CRO rather than duplicating services. Avoid redundant overlapping and let the CRO use its global infrastructure and expertise to work with the SP in developing and executing the plan.

Dr. Thomas Frey: The CRO should be able to span the whole range of services from compound selection, to IND, clinical development, and finally to submitting an NDA. The expertise in the drug development process should be available to Specialty Pharma, either on a full-service basis or in niche areas where the Specialty Pharma company needs support because of its in-house skill gap.

Dr. Thomas Smith: Specialty Pharma expects a true development partner with the resource flexibility and the clinical know-how to deliver development programs. As such, the CRO partnering with a Specialty Pharma company should champion the development program for the Specialty Pharma's product. In particular, to maximize efficiencies, the CRO team should be intimately familiar with the product or compound to be tested, the competition, the regulatory environment, the development strategy, and the desired product label. The CRO team should identify potential concerns with the development plan and offer alternative approaches when appropriate, providing added value to the Specialty Pharma. Setting clear expectations from the start regarding project deliverables as well as roles and responsibilities fosters ownership and trust.

Dr. John Potthoff: There are three key deliverables that a Specialty Pharma company should expect from its selected CRO: execution, therapeutic expertise, and product development expertise. First, a CRO should always execute and deliver according to plan and program outlines established at the onset of a project. An SP company should select a CRO based on its ability to follow deadlines and efficiently offer expertise in the type of trial and therapeutic focus area. This criteria helps ensure that the CRO has the experience and ability to execute the trial according to plan. Second, a CRO should provide therapeutic foresight demonstrating the ability to provide input into the specific therapeutic focus of the clinical trial. A Specialty Pharma


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company should select a CRO based on its expertise in a specified study area so that the CRO can offer the best methods of development, progression, and completion of its project. Ultimately, a CRO should have a vast amount of hands-on experience in a given therapeutic area for the SP's clinical trial focus, thereby assuring confidence in the team. Third, an SP company should always expect the CRO to have product development expertise. Product development expertise ensures that the CRO is well versed in creating clinical development plans, providing a trusted source for information and consultation, and offering critical regulatory experience. A product development team is instrumental to the planning and progression of the trial, ensuring that the trial moves forward on time and on budget with strategies in place to tackle any potential obstacles.

Dr. Larry Meinert: A Specialty Pharma company ultimately expects that the CRO delivers on the timely completion of a clinical trial or program on time, on budget, and with acceptable quality. In order to realize this expectation, the CRO must then be able to develop a reasonable plan how to get the job done with the full cost and timelines of the most likely performance scenario rather than the too short and less expensive optimistic scenario; manage well-selected sites that can enroll and follow the protocol; and undertake proactive efforts to predict performance risk with mitigation in addition to the activities encompassed in conventional statement of work. These conventional activities typically involve managing the logistics of the trial and the ongoing activities to verify and trial data and to repair any deficiencies notes by monitoring or data management.

Q: Please describe how CROs and SP companies together can save time in clinical development.

Dr. Thomas Smith: From the beginning, there should be an open sharing of information between the CRO and the SP company. The CRO team needs to be fully familiar with the product or compound. Ideally, this would begin with establishing a core project team at the CRO who would serve as the Specialty Pharma's consistent point of contact throughout the development program. This helps establish continuity and history for the project. The CRO team must be brought up-to-date as quickly as possible with regard to recent advances in the science, the therapeutic area, and the Specialty Pharma's product, as well as the company's business drivers (e.g., timeline requirements) and desired label. Likewise, the CRO should be open and up-front with the SP company, providing feedback and initial impressions on desired timelines, patient recruitment issues, and other important issues. Addressing issues early on in a constructive manner often alleviates future delays.

Dr. John Hubbard: The biggest challenge in clinical development is patient recruitment. Significant technology enhancements have been made in data acquisition; however, the rate-limiting step in the process of completing a trial is still patient screening and enrollment at the site level. A CRO that knows the competitive environment for patient recruitment in clinical trials can work with SP companies to identify the best regions and sites to optimize patient recruitment. The CRO can also provide critical input to the protocol inclusion/exclusion criteria that will maximize the probability of technical success.

Dr. Larry Meinert: In the current clinical research environment, according to CenterWatch, more than 90% of clinical programs are behind schedule. It is reasonable to assume that few CROs awarded a program ever promised to deliver a program behind schedule. "Competitive optimism" is what often differentiates one CRO from another. In almost 90% of the cases, the assertions made by the winning CRO prove to be ill founded. The single most important way to save time is for both parties to be honest about the challenges that face the project and jointly address them proactively. Today, "inconvenient truths" are swept under the rug, and projects start out on a false note. More than 90% of the time this leads to failure. The simple answer to this question is to tell the truth.

Dr. Mark A. Goldberg: Advanced planning is key to running a time-efficient and cost-effective clinical trial. It's critical that the service provider understand the results that the Specialty Pharma company is trying to achieve and construct a customized drug development plan to meet those objectives. That means understanding what the Specialty Pharma company's goals are from a market and geographic perspective and overall what they want to accomplish at the completion of the development program.

Dr. John Potthoff: Most projects lose footing when there are not clear expectations communicated for the outcome of the project. At the beginning of each trial, the sponsor and CRO need to establish project expectations and timelines so the entire team is progressing toward the same goal. Oftentimes, unmatched expectations are the most significant roadblocks to staying on time. This disconnect between the onset and strategic endpoint of the project often results in additional time and costs due to the need for redirection. Thus, ongoing, clear communication between CROs and SP companies is key to successful, on time clinical development. Additionally, SP companies should utilize the standard operating procedures (SOPs) and processes used by their CRO. By utilizing the SOPs and processes in practice by the CRO, the project can start off ahead of the timeline and take advantage of the best practices found to work for the CRO. Finally, it is critical that there is ongoing and constant communication between the CRO and the SP company throughout the length of the project. This enables each team to address issues and create solutions immediately without delaying the project. A key step to ensuring this

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constant communication is to establish milestones or triggers that require communication between the teams.

Dr. Thomas Frey: The areas where significant time can be saved are the decision-making process and patient recruitment. A clearly laid out drug development plan with the end in mind, i.e., the planned label, will help define objectives for study protocols and inclusion/exclusion criteria. Typically, the CRO gets involved late in the execution of studies where very little influence is possible on protocol design and hence patient recruitment. A joint Specialty Pharma and CRO project team could come up with a straight-forward development plan and study synopses, which if implemented, would result in expedited conduct of studies and patient recruitment.

Mr. Jeff Thomis: The most important step is to define the "end game." What is the goal of the clinical program? Don't rush into setting up the study until you know the goal, then work backward from there. Meet with regulatory authorities to determine their regulatory needs. Establish milestones. And consider options — would a program to gain approval in a niche indication be a faster course to the market than going after a broad-based indication? Planning up-front will save time by keeping the development team focused and avoiding missteps along the way. With a successful plan in place, both the CRO and the customer should then manage performance, assuring that both the CRO and the sponsor company reach their milestones on time.

Q: What are the infrastructure requirements for a SP company to best work with a CRO? That is, what in-house personnel does SP really need?

Dr. John Potthoff: Ultimately, if the SP company is specifically focused on getting a product to market immediately, there are no special infrastructure requirements necessary to work with a CRO. For the most part, the CRO should have the infrastructure in place to successfully complete the project. It is not uncommon for the CRO to interface directly with the CEO of an SP. SPs understand that their valuation comes from moving products through development, not from building processes.

Dr. Larry Meinert: The best model for a Specialty Pharma to follow is to adopt the role that a well-educated concerned family member adopts when their mother is diagnosed with breast cancer. They do their homework and help drive a very careful selection of provider. They drive to provide a dispassionate support in helping to anticipate issues and make sure that the right questions get asked along the way. However, they do not interfere with the administration of therapy. Their engagement does make a difference in the overall quality of care. The Specialty Pharma industry brings to bear a similar perspective. At minimum, a staff member with a project management background can act in the patient advocate type role on behalf of the project. They function best when they are oriented to preventing problems and refocusing others on the bigger picture development strategy rather than being immersed in tactical detail second guessing the CRO. However, if something is just plain wrong, there should be no hesitancy to forcefully speak up. It is also important for the SP company to have a drug development scientist who can speak with an authoritative voice to make definitive medical/regulatory judgments on the sponsor's behalf in rapid fashion. IT connectivity and data transfer issues always arise in new relationships. An IT liaison is crucial. Ultimately, money anchors a collaborative transaction. A very engaged contract person who is averse to early contract ambiguity serves the interests of all.

Dr. John Hubbard: The SP company needs a small team consisting of a scientific/technical manager and project manager who can communicate effectively with the CRO and provide the SP companies a vision of the product. The CRO can provide the other elements, but open and clear communication is critical. Most issues arise from misunderstandings or unclear expectations. The most successful programs are the result of a good working relationship between the SP company project manager and the CRO project manager. I also recommend that senior management from both organizations form similar relationships and even serve together on a joint steering committee to help guide the product development program.

Dr. Dennis P. Hurley: A true full-service CRO can take on as much or as little of a project as needed, or even handle a full drug development program, depending on the customer's needs. Therefore, it is possible that a customer can actually have very few in-house personnel and still develop a drug successfully. There are a number of good examples of Specialty Pharma companies doing this recently. Having said that, the in-house personnel the Specialty Pharma does have are extremely valuable to the program because they have full access to all of the Specialty Pharma's project and corporate goals. Also, in-house personnel often have a long history with the Specialty Pharma that facilitates work and decision-making as the program progresses with the CRO.

Mr. Jeff Thomis: Sponsors should not try to mirror the CRO or set up to micromanage the CRO. The CRO selected should have the experience and expertise to successfully conduct the clinical program; the sponsor needs to make sure that the CRO is performing as planned and is hitting its milestones according to plan. The sponsor then can focus on its investors and working with regulators toward approval without using its limited resources to duplicate what the CRO is already doing.

Dr. Thomas Frey: In-house personnel from the SP company who are empowered to make decisions and sign-off of protocols, reports, site selections, budget, and issue resolutions as these arise.

Dr. Mark A. Goldberg: It is helpful for an SP company to have at least a few in-house professionals with significant drug development experience. These professionals can work with the service provider partner to help guide the strategic direction of the program and participate in important decisions.

Q: What are the keys to developing clinical trial data that allow it to be effectively used in different world markets?

Dr. Mark A. Goldberg: A product development strategy must map the markets that a company is targeting. To design an effective program requires a deep understanding of the regulatory processes in the various countries in which the drug will be marketed. That insight helps ensure that the right data is collected to support drug approval in target geographies. Regulatory authorities in different geographies have unique requirements and expectations. Therefore, it's important to have experts who can act as regulatory agency liaisons and develop regulatory compliance strategies with Specialty Pharma companies during the early stages of the drug and clinical development process. It is important that these experts have a deep understanding of regulatory affairs and have contacts within the regulatory authorities to get appropriate guidance for the study. We have found that ex-regulators can serve as highly valued consultants, and we employ many of them within our organization.

Dr. Dennis P. Hurley: ICH-GCP compliance is the most important factor. In addition to obtaining the fastest possible approval, it is important to consult with the major regulatory bodies like the FDA and EMEA during the program to ensure their needs are fully met. Most of the smaller countries' needs will be met if the FDA and EMEA requirements are met.

Mr. Jeff Thomis: Any clinical program that develops data for use in different markets must comply with Good Clinical Practice (GCP) guidelines. GCP guidelines provide the internationally recognized framework for globally accepted clinical trial data. Even with GCP, the key to developing good clinical data is communication – particularly with regulators, including the FDA, EMEA, and Japan's Ministry of Health and Welfare. Understand their needs and concerns before developing the clinical program, and then establish milestones and endpoints that will meet those needs and concerns. A global CRO can also help an SP company identify any needs of a particular market – use the CRO's experience.

Dr. John Hubbard: It is imperative that both the SP company and CRO understand the regulatory and commercial differences of medical practice, product usage, and marketing around the world. For example, a certain dosage form may be very accepted in Europe, but not as readily accepted in Asia. Consequently, a sound knowledge of the prescribing patterns in the region along with any cultural biases around formulation or delivery technology is important. Another area that is becoming increasingly important is the area of pharmacogenomics and impact of diet on drug absorption, safety and efficacy, metabolism, and elimination.

Dr. Larry Meinert: The growing issue with the effective global use of trial data is whether the generalizability holds no matter where the trial is conducted. The historical challenge was around whether if data generated in Western Europe could be used in the US and visa versa. That extended to data from Central and Eastern Europe and Latin America. However, in some therapeutic indications, patient recruitment must extend to the farthest corners of the earth because protocol inclusion/exclusion criteria call for patients who cannot be found in the western markets. To the extent this refined selection of patients carries over from Phase II trials to Phase III, the greater the risk a problematic market application. The key is to balance geography and patient selectivity. A mix of countries and reasonably open eligibility criteria will, in the long-term, maximize effective global use of trial data.

Dr. Thomas Frey: The data acceptable to different markets need to be based on sound study protocol designs, statistically adequate powered studies, ethnically balanced study populations, clearly defined primary and secondary study objectives, adherence to patient selection criteria, and ultimately quality data, which are analyzed according to ICH agreed standards.

Dr. John Potthoff: Critical trial data can be effectively used in different markets by utilizing data warehousing tools early in the development of a product. This approach enables the easy use of data sets for various submissions and partnering in a world market. Data, as the critical element in the drug development process, can increase at a rapid rate and oftentimes, the resources to support the volume and integration of data generated are not in place. Many biotech and pharmaceutical companies have identified the need for a flexible solution to store and manage crucial data, without resorting to costly internal development.

Q: Can you share a success and/or defeat you had when working with a client?

Mr. Jeff Thomis: In a successful relationship, the CRO and sponsor's goals are aligned, communication is good, and trust is established. A good relationship starts with clear goals, a clear plan, and clear milestones. An unsuccessful relationship has no alignment. In one case, Quintiles was used

only as an "arms and legs" CRO and was micromanaged. There was no understanding of the end game, and we were asked to do things in total isolation of any plan. The project became a fiasco.

Dr. John Hubbard: We provided full development services support to an SP company developing a chronobiology dosage form to optimize the peak levels of a beta-blocker during the early morning hours. It has been shown that most heart attacks occur in the early morning hours when peak levels of cardio-protective drugs may be at their nadir. Consultation on the study design, country, and site selection enabled us to meet the SP company's timeline objectives for patient enrollment.

Dr. Mark A. Goldberg: We worked with a small pharmaceutical organization to undertake 17 studies, involving more than 2,000 patients, ranging from Phase I to III to examine a novel AIDs/HIV treatment. PAREXEL assisted this company in taking the drug from the laboratory to new NDA approval in only 3 years, one of the fastest drug development times in FDA history.

Dr. Dennis P. Hurley: A success: A Specialty Pharma working with Kendle was able to go from first-in-human to Phase II trials fully enrolled with successful interim analyses in 16 months. This success led to the Specialty Pharma securing a major ($500 million+) licensing agreement with a large pharma company. The key success factor was getting started in Latin America and then getting the IND to also enroll in the US. As a result of our global reach and local expertise, specifically our on-the-ground experts who dealt with local customs, regulatory bodies, and suppliers, the project was able to get up and running quickly. A failure: In an oncology development program, Kendle consulted with a Specialty Pharma that was ready to begin its Phase III trial. Kendle's Patient Access and Retention team presented a report showing a multinational (US, Central and Eastern Europe, and Latin America) solution was needed to enroll in the desired timeframe (about 9 months). The same report stated that a US-only option would enroll three to four times more slowly. The Specialty Pharma received a proposal from another CRO that stated that a US-only solution would be successful and more cost efficient due to less sites and not going international. The Specialty Pharma contracted with the other CRO. A year later, the trial was less than 25% enrolled in the US. Unfortunately, the Specialty Pharma now faces serious economic difficulties. At the same time, Kendle undertook a similar trial in the same indication using a multinational (US, Central and Eastern Europe, and Latin America) solution with a full patient access and retention component. This trial finished enrolling several weeks ahead of schedule. The US enrollment was approximately 10% of the total global enrollment, as had been predicted by Kendle's Patient Access and Retention group. This company is working on filing its NDA.

Dr. Larry Meinert: One of our greatest successes with an SP company is when we were forthright with them about the challenge associated with their Phase III program as our competitors proposed meeting aggressive timelines. We ultimately won, but persuaded the sponsor to limit its financial commitment until the trial was underway and the chance for success optimized and projections recalibrated. In the end, the sponsor agreed that our assessment was correct and it cancelled the program and redirected their funds to more promising agents. We have learned that it is especially important for an SP company to live to fight another day if a particular agent is not succeeding. Our greatest defeat occurred when we recognized a very challenging undertaking, but became so enamored of our mitigation measures we fell back into competitive optimism. We have learned that in certain circumstances, every reasonable effort is not enough to assure meeting unrealistic expectations.

Q: What are the pros and cons concerning clinical trials in emerging market countries?

Dr. John Hubbard: There are many advantages and challenges to conducting clinical trials in emerging markets. Government bureaucracies, regulatory approval timelines, high costs for importing/exporting drugs, cultural differences in the perception of due diligence, mandatory generic prescribing, counterfeit medicines, protecting intellectual property, and assuring that investigators comply with international ethical standards are some of the many challenges facing researchers in these regions. One of the biggest advantages to conducting research in emerging regions is the huge number of treatment-naïve patients, especially in metropolitan centers. Other advantages include rapid investigator and patient recruitment — patients are eager to gain access to modern diagnostic procedures, medicines, and care, and investigators want to be involved in leading-edge research. Speed of enrollment advantages and potential cost savings also make conducting studies in these regions very attractive. Establishing successful operations outside of the US and Europe can be challenging. A lot of skills come into play, including cultural awareness and language skills. The secret of success is having a working knowledge of the region, working hard at establishing close relationships with key opinion leaders, and building a strong network of motivated investigator sites.

Dr. Dennis P. Hurley: Major advantages of adding emerging market countries to a trial are the speed with which patients can be recruited. Also, there are usually cost savings that may be substantial depending on trial design. The major challenges in emerging markets can be overcome by working with a CRO offering broad multinational coverage; a strong Patient Access and Retention group with demonstrated success in country and site

selection and successful execution of patient recruitment and retention programs; and strong local leadership and knowledge in each country chosen for the trial so that regulatory timelines can be met and logistical issues successfully addressed.

Dr. Mark A. Goldberg: Working in emerging markets affords access to large populations of patients. In general, it is less expensive to recruit for patients in these geographies. It is also often easier to find patients in emerging geographies that fit certain study specific profiles. One concern that's often expressed when considering emerging geographies is data quality. Working with a partner with a well-established infrastructure, strict quality oversight, and experience with particular investigator sites can help to ensure data quality. It is not easy for any pharmaceutical company to conduct clinical research in emerging geographies if they don't have the requisite experience and a local presence. Partnering with a service provider that offers this local experience and an established presence is key for success.

Mr. Jeff Thomis: The pros of conducting trials in emerging markets are many – an abundant number of patients, investigators who are highly trained and keen to be involved in clinical research, and in most cases, good, sophisticated medical infrastructure and patients keen to have access to new therapies. Some emerging markets, however, still have long approval times for clinical projects, which can actually slow down a program rather than save time. Some investigators may not be experienced in certain techniques. An experienced, global CRO knows when a particular market fits a plan and when it does not.

Dr. John Potthoff: Conducting trials in emerging market countries has several potential benefits. Emerging market countries often provide access to a group of patients that would not otherwise be available. For example, it may be necessary to choose a market in which a competing compound is not available. These markets also extend the calendar for seasonal diseases such as influenza. With the technology now available to manage data collection across the globe, emerging markets are more accessible because we can now collect data worldwide without altering our data infrastructure. Alternatively, the challenges associated with clinical trials in emerging market countries are regulatory and legal delays. These obstacles can be mitigated by integrating the needs for the country into the initial project plans rather than as an afterthought or rescue measure.

Dr. Thomas Frey: The data collected and generated in emerging markets need to be comparable to and "extrapolateable" to the western country standards and population characteristics. For example, there is a tendency for higher responses to placebo in some emerging market countries in CNS/psychiatry indications compared to western countries. This may lead to less favorable results in clinical studies in these indications.

Q: Please offer tips on how an emerging SP company can get the attention it deserves (and pays for) when working with a larger CRO.

Dr. John Hubbard: I believe many larger CROs see SP companies as important clients because they tend to have development programs with a higher probability of technical success. They look at new uses for older drugs or alternate dosage forms that optimize delivery of the drug to the target area. Consequently, there can be less risk to the CRO that the drug will fail and thus, more chance to continue development services. It is important that the SP company select a CRO that is client focused and collaborative. A large CRO can provide better support to the SP company as long as its attitude and culture support a collaborative working relationship.

Dr. Martha R. Feller: CROs seek to build their customer base within their core competency areas regardless of customer size. A Specialty Pharma company should partner with a CRO that has a successful track record in its relevant therapeutic areas. Furthermore, the Specialty Pharma should look for a partner offering experience and capabilities in the regions of the world providing the patient population needed for their trials. For instance, a Specialty Pharma developing a diabetes drug would want to partner with a CRO with a successful track record in endocrinology as well as strong infrastructure in Latin America. This would ensure that the CRO has the proper clinical experience and expertise as well as access to the right patient populations.

Dr. Larry Meinert: The most important tip is to focus the discussion therapeutically. The discussion should then center on self competition. How many concurrent trials is that CRO signed up or signing up to do that directly compete for patients or study personnel? What is the nature of CRO staff "exclusivity" within this competitive zone as well as the exclusivity on site selection? Is the CRO constrained from going to all potential sites? Openness within the limits of confidentiality should be demanded.

Dr. Thomas Frey: Apart from the financial remuneration, the CRO teams tend to work more effectively together with clients who engage closely with the CRO, meaning involving the CRO in the information sharing and decision-making process. This creates a work environment in which the CRO feels part of the development process and adding value, which in turn translates in improved motivation, speed, responsiveness, and quality.

Dr. John Potthoff: The level of attention afforded each customer, for an emerging or established SP company, will be high regardless of the size of the CRO as this is the

nature of our business. However, the SP's critical resource at a CRO is the Project Manager. Because project management is critical to the success of a trial, it is advisable for the SP company to budget for as much project management as they can afford. Budgeting for a dedicated project manager ensures that the person's focus is solely on your trial.

Mr. Jeff Thomis: The SP company should look within the CRO for a specific unit or group of people who understand the needs of an SP, particularly if the CRO has people who once worked for an SP company. Communication is crucial in any relationship. Planning up-front – setting clear goals and milestones – will get the relationship off to a good start. Establishing a trusting relationship will keep lines of communication open and ensure any problems are dealt with quickly and openly.

Dr. Mark A. Goldberg: Choosing the right service provider partner is the most critical factor, especially for an emerging Specialty Pharma company, to ensure it gets the level of attention it deserves. Historically, the CRO industry was focused on working with large pharmaceutical companies, but this has shifted significantly toward small and emerging companies. We believe that success in working with Specialty Pharma clients requires a cultural change. It means a deeper sense of ownership and accountability, and a much more proactive approach to problem-solving. The sponsor/provider relationship is best characterized as a partnership focused on the success of the development program. ■

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Facts & Figures

Bionumbers: Specialty Pharma Market Indices

Index Trends

February saw another reversal in trends for the two indexes. The *Commercial Stage Specialty Pharma Index* (CSP) gave back some of its January gains, about 1%, for a year-to-date increase of 4%. February results for the Emerging Stage Specialty Pharma Index (ESP) were more positive, up about 4% over January, but still behind about 1% year-to-date. At the time of writing, March 23, both indexes are showing a flat or slight decrease for the month, consistent with the softness of the major stock indexes.

Commercial Stage Index Trends

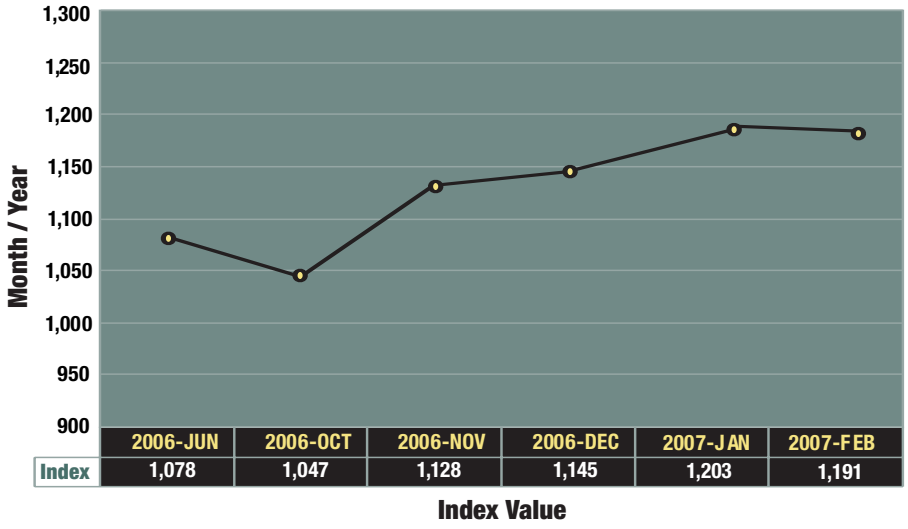
The CSP Index was basically flat for February. Hospira, King, and Endo all held onto their double-digit growth for the year, while Shire was up a solid 4%. Abraxis was flat through February, but seemed to be starting to bleed a little in March. Among the laggards, both Columbia and Advancis showed huge losses in market capitalization. Index capitalization was down about $600 million from January, but up $2.3 billion over December when adjusted for the departures of CoTherix and Kos.

Emerging Stage Index Trends (ESP)

The ESP Index showed some bounce back in February, largely due to the take out offer for New River. If not for this, the market would be down almost 7%. Nektar and Penwest, given their larger contributions, were largely responsible for the index losses, although Scolr (-28%) had the largest year-to-date loss. Capitalization for the index dropped to $6.9 billion from $7.3 billion at the end of December. ■

Bionumbers Commercial-Stage Specialty Pharma Index

FEBRUARY 2007



Key Figures February 2007
Index Value: 1191
Change YTD: +4.0%
Total Index Capitalization: -$59.0 Billion

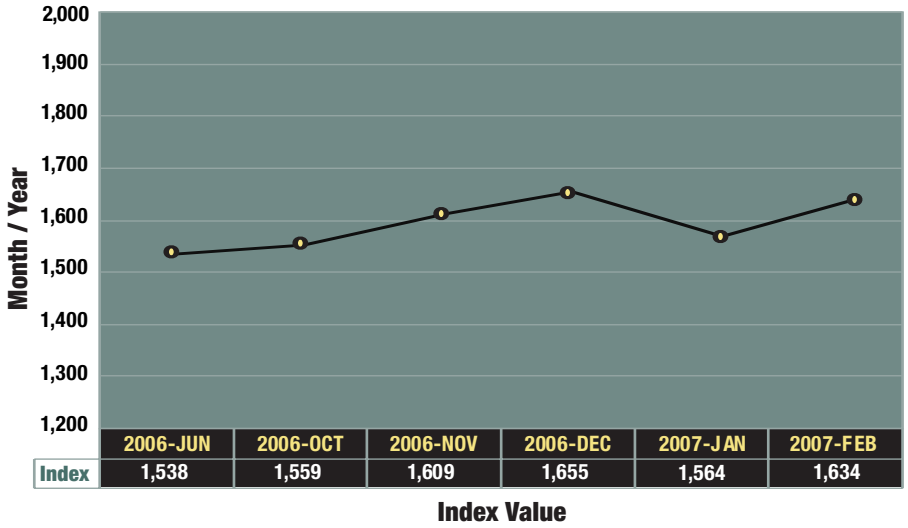
Top 5 Gainers YTD Change	
Vivus	+31%
Collagenex	+17%
King	+17%
Alkermes	+17%
Ista	+15%

Top 5 Laggards YTD Change	
Columbia Labs	-72%
Advancis	-36%
Avanir	-20%
Angiotech	-19%
Novavax	-19%

Top 5 Capitalizations YTD Change		
Shire	$10.9 Billion	3%
Hospira	$6.0 Billion	12%
King	$4.5 Billion	17%
Abraxis	$4.4 Billion	0%
Endo	$4.2 Billion	13%

Bionumbers Emerging-Stage Specialty Pharma Index

FEBRUARY 2007



Key Figures February 2007
Index Value: 1634
Change YTD: -1.3%
Total Index Capitalization: $7.3 Billion

Top 5 Gainers YTD Change	
New River	+20%
Cadence	+20%
Spectrum	+16%
Epicept	+13%
Acusphere	+11%

Top 5 Laggards YTD Change	
Scolr	-28%
Nektar	-21%
Penwest	-21%
Somaxon	-20%
NovaDel	-14%

Top 5 Capitalizations YTD Change		
New River	$2344 Million	+20%
Nektar	$1084 Million	-21%
Aspreva	$771 Million	+5%
Keryx	$496 Million	-14%
Cadence	$414 Million	+20%

Partner or Competitor?: Japan Pharma Making Its Mark in the US

By: Keith Morton, MBA, President, Erimo Consulting

Introduction

To say that the world has changed in the past 10 years is trite beyond extreme. But we often forget just how much things around us are different today than they were in 1997. The presence of the Japanese pharmaceutical companies here in the American market is just such a case. As shown in Figure 1, in 1997, just a single Japanese pharmaceutical company was listed in the Physician Desk Reference (PDR), and it (Fujisawa) had only one listing. Compare that to today. There are 5 Japanese pharma companies (it would be 7 if not for the mergers of Fujisawa-Yamanouchi and Daiichi-Sankyo) with 26 listings in the 2007 PDR.

This has a couple of implications for the rest of the industry. If you are a business development executive for a major pharma company, your source of potential blockbuster compounds from the large Japanese pharma companies has shrunk throughout the past 10 years and will continue to shrink in the coming years. Also, with the emergence of more of these companies as mid-major or major players, here in the US, the competition for talent, for share of doctors' time, for market share, etc. will continue to increase. If you haven't already started to approach these companies with a different mind set, now is the time to start thinking about it.

How Japanese Companies Enter the US Market

In the past, Japanese pharmaceutical companies have taken a fairly proscribed approach to entering the US market. They began by establishing a small group consisting of ex-patriot Japanese with maybe a couple of local hires to do in-licensing, out-licensing, and managing of CROs for the few compounds that had been designated for US development. At this point in their development, Japanese firms often out-licensed their compounds to larger pharma

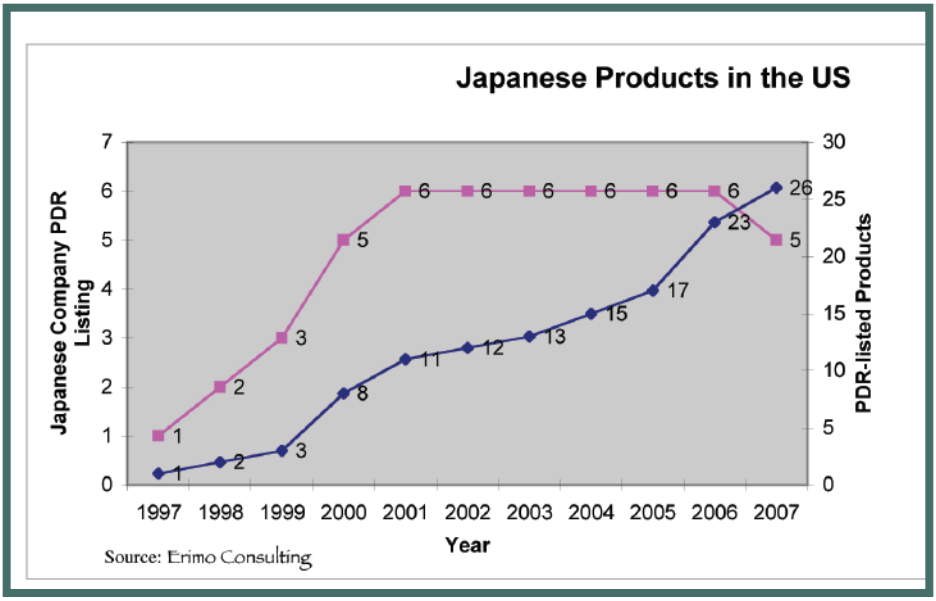


Figure 1.

COMPOUND	ORIGINAL OWNER	PARTNER IN USA	TYPE OF RELATIONSHIP
Flomax	Yamanouchi	Boehringer Ingelheim	License
Prevacid	Takeda	TAP (Takeda-Abbott JV)	License
Ablify	Otsuka	BMS	Co-Marketing
Actos	Takeda	Eli Lilly	Co-Marketing
Aricept	Eisai	Pfizer (Roerig)	Co-Marketing
Benicar	Daiichi Sankyo	Forest	Co-Marketing

Compiled by: Erimo Consulting

Figure 2.

companies operating here in the US. After years of operating in this model, the firms would then increase their US presence with more local hires, the most important being the head of R&D/clinical. The clinical department would increase, and the companies would take the compounds from IND submission up through Phase IIb. At this point, they would begin to work with those companies with a major presence in the US as more of a partner, albeit a decidedly unequal one. For the first couple of compounds, they would co-promote or co-market the compound with an established player in the US. This model would mitigate some of the risk of failure incurred by the costly phase III trial. Of course, the price that came with this risk reduction was a diminution of upside potential. Some very successful products are examples of just this type of partnering — Abilify, Benicar, and Prasugrel. Figure 2 shows those notable marketed ethical pharmaceuticals that originated in the labs of Japanese pharma companies, but were brought to market wholly or in part by established players in the US.

By the third or fourth compound, the Japanese company would have built its own sales and marketing department and take the compound to market under its own brand, and therefore be seen in the PDR. In addition to clinical milestones, as the Japanese companies here in the US grew, there were a few key organizational milestones worth mentioning.

At the time of the hiring of the local clinical/R&D head, the only other senior management member would have been the ex-patriot Japanese president of the US affiliate. The next hire was most likely the head of HR. This usually occurs before the first co-promotion with a major pharma. The next three major management additions — head of sales and marketing, head of IT, and legal counsel — happen at roughly the same time. The final piece of the management team is the CFO. One model has it that as the Japanese president returns home after his rotation and is replaced by a local president, an ex-patriot senior executive, (CRO, chairman, CEO) arrives from Japan, keeping control at least partly back in Japan. Finally, all senior management is in place, and they are all local hires reporting into Japan, but with a great deal of autonomy. A quick look at the organizational chart of the Japanese pharma's US affiliate will give a good indication of the company's maturity here in the market.

Please note that the aforementioned model is the general framework used by the Japanese companies. However, as all companies are different in their risk tolerance, business models, management styles, resources, etc., the model will not fit universally throughout their entire growth.

Currently, the time it takes to go from having only a local clinical/R&D head to having all senior management as local hires is being compressed. Looking at Figure 3, we see the top five (by revenue) Japanese pharma companies are already very active in the US marketplace. The hypothesis is that the next group of companies is moving rapidly to follow their larger brethren.

The major reason for this increased US affiliate presence can be attributed to a continued depressed domestic market in Japan. As stated in the Ono Pharmaceutical flash report, "The Japanese pharmaceutical industry labor[s] under a continuing, harsh business climate associated with the government's enforcement of various medical cost-containment measures and intensified by market competition among Japanese and non-Japanese companies." For many years, government cost control and weak economic operating conditions in Japan have weakened the domestic pharma industry. Those firms that have a large, mature presence here in the US reacted to the weak domestic market by diversifying in the markets they serve. One could imagine that the late-adopters were betting on the eventual reversal of the Japanese

Top 15 Japanese Pharmaceutical Companies

	FY 2005 Revenue ($millions)	FY 2005 R&D Spend ($millions)	PDR Entries
Takeda	$10,361	$1,450	5
Daiichi Sankyo	$7,914	$1,343	5
Astellas	$7,516	$1,214	9
Eisai	$5,139	$797	4
Otsuka	$3,300	$490	3
Chugai*	$2,796	$428	n/a
Taisho	$2,320	n/a	-
Dainippon Sumitomo Pharma	$2,101	$253	-
Mitsubishi Pharma	$2,019	$410	-
Shionogi	$1,678	$276	-
Tanabe	$1,466	$261	-
Ono	$1,271	$286	-
Kyowa Hakko	$1,157	$239	-
Taiho	$1,068	$243	-
Meiji Seika Kogyo	$986	n/a	-
Asahi Kasei	$904	n/a	-

*Chugai is a wholly owned subsidiary of Roche. Revenue numbers are included because they are made available as such. Source: Erimo Consulting

Figure 3.

economy to lift their economic fortunes so that they would not need to turn their focus from the domestic market. However, the Japanese government's focus on reducing healthcare costs and the significant biennial NHI drug price reductions cannot be written off as merely a passing phase, and this has pushed those firms toward global markets, especially the US, much faster.

Some of the top 15 Japanese pharma companies are smaller divisions of large companies, e.g., Meiji Seika and Asahi Kasei are part of much larger food, beverage, and chemical companies Meiji and Asahi, respectively, and are under slightly less overt market pressure, as the other, larger divisions can help subsidize the pharmaceutical business. The other companies, however, have responded to this pressure in a couple of different ways — merger/acquisition for domestic scale and faster international expansion in a look for new revenue sources. Examples of the first include Astellas (Fujisawa and Yamanouchi), Daiichi-Sankyo Pharma, and Dainippon Sumitomo Pharma. Examples of faster international expansion and greater global aspirations can be seen in a number of companies. This is not to say that overnight all Japanese pharma companies will become truly global entities and that all co-marketing deals or out-licensing deals from the Japanese pharma companies will come to an end. For example, the phase III study for Prasugrel, Daiichi-Sankyo's ADP receptor antagonist, is being conducted in cooperation with Eli Lilly. The following trends, statements by leadership and current examples, however, lead one to believe that the Japanese companies are moving at a rapid pace in the direction of globalization (Figure 4):

- Kyowa Pharma is planning on taking Istradefiline to market as soon as it receives FDA approval and does not have a marketing partner.

- In November 2006, Mitsubishi Pharma acquired the exclusive global development and commercialization rights to Kremezin, including the US, but excluding Japan, South Korea, China, Taiwan, the Philippines, India, and Israel.

- In a December 2006 press release, Dainippon Sumitomo Pharma "succeed(ed) the overseas clinical development of Lurasidone from Merck and has already started its review of the clinical development program to be continued by DSP in the US…"

- Tanabe states on its website that, "(They) are making steady progress in the construction of our own in-house development system overseas, with a view to establishing independent sales capabilities in Europe and the US."

- In his message on the corporate website, Motozo Shiono, President of Shionogi, states, "We are striving to make our operations more sophisticated, more efficient, and more global in all fields, ranging from research and development to marketing. We will put forth the greatest effort possible to…become a corporation with a strong presence worldwide."

- Daiichi-Sankyo's Vision 2015 is to be a "Global Pharma Innovator" with two of the key points in its mid-term management plan being a

Top 15 Japanese Pharmaceutical Companies

	FY 2005 Revenue ($millions)	PDR Entries	Comments
Takeda	$10,361	5	Continued growth in US
Daiichi Sankyo	$7,914	5	Continued growth in US
Astellas	$7,516	9	Continued growth in US
Eisai	$5,139	4	Continued growth in US
Otsuka	$3,300	3	Continued growth in US
Chugai*	$2,796	n/a	Growth in US will be under parent name (Roche)
Taisho	$2,320	-	No publicly available information
Dainippon Sumitomo Pharma	$2,101	-	Lorasidone
Mitsubishi Pharma	$2,019	-	Kremezin
Shionogi	$1,678	-	Already markets CEDAX® a 3rd generation cephalosporin antibiotic here in US
Tanabe	$1,466	-	TA-6666 (Phase II in US)
Ono	$1,271	-	No publicly available information
Kyowa Hakko	$1,157	-	Istradefiline
Taiho	$1,068	-	No publicly available information
Meiji Seika Kogyo	$986	-	Small division in a larger non-Pharma company
Asahi Kasei	$904	-	Small division in a larger non-Pharma company

*Chugai is a wholly owned subsidiary of Roche. Revenue numbers are included because they are made available as such. Source: Erimo Consulting

Figure 4.

target for 2009: having 40% of its sales from overseas and to strengthen its sales performance in the US by increasing the number of medical reps by a factor of 2.5.

- Otsuka Pharmaceutical announced in January 2007 the formation in Princeton, NJ, of Otsuka Pharmaceutical Development & Commercialization Inc. that "…is the cornerstone of Otsuka's global drug development and strategic commercial planning efforts."

Summary & Conclusion

So what does this all mean for the industry here in the US? It certainly suggests that what in the past may have been seen as a source for in-licensing or at the very least a co-marketing deal to add to your portfolio of compounds now must be viewed as a full-fledged competitor within the therapeutic areas in which they choose to play. Our already competitive pharma industry here in the US is going to continue to get even more competitive.

Back in 1997, who would have thought that within 10 years the Japanese pharma companies would have made the inroads into the US that they have? It will be interesting to see where the next 5 years will lead us, let alone the next 10. ■

Keith Morton, MBA

Erimo Consulting

Mr. Keith Morton is President of Erimo Consulting, a global strategic management consultancy that he founded on the belief that "consultant" doesn't have to be a bad word. Mr. Morton and his colleagues have worked with some of the world's best pharma, biotech, and diagnostic companies, as well as suppliers to those organizations. He is a seasoned management consultant, having worked more than a dozen years based in the US, Europe (France and Switzerland), and Asia (Japan, Taiwan, and Singapore). Mr. Morton has helped organizations of all sizes handle complex challenges of strategy development, strategy implementation, executive alignment, and coaching. Erimo's specific areas of expertise include clinical efficiency and partnering, business development, strategic alliances, new business initiatives, and marketing and sales. Mr. Morton earned his BA in economics from Union College and his MBA from The Anderson School at UCLA. He is currently Membership Director for the NY/Tri-State Chapter of the Association of Strategic Alliance Professionals (ASAP). Mr. Morton can be reached at keith@erimo.com.

Executive Summary

Mr. Mohan Bhandari
Chairman & Managing Director, Bilcare Limited, India

Mr. Steven Jacobs
President & Global Chief Operations Officer, Bilcare Inc., USA

Bilcare: Perfecting Drug Packaging for its Customers

By: Cindy H. Dubin, Contributor

Bilcare Limited, headquartered in Pune, India, is a unique organization with a strong research foundation, integrated with the global pharmaceutical industry. It has established a state-of-the-art barrier polymer processing facility to produce innovative multi-layered barrier films for use in primary packaging of solid pharmaceutical dosage forms. The company's unilateral focus on pharmaceuticals and its in-depth understanding of the needs, functionality, quality, and safety requirements of medicines led to the pioneering of norms, specifications, manufacturing practices, and quality standards establishment for packaging materials coming in direct contact with drug products. Mr. Mohan Bhandari, Chairman and Managing Director of Bilcare Limited, and Mr. Steven Jacobs, President of Bilcare Inc., USA, explain that with three major research and operations facilities and three regional offices (Latin America, Europe, and China), Bilcare has an exclusive focus on pharma packaging solutions, facilitating the life science industry in the value chain from drug discovery to market.

Q: ***Can you briefly explain Bilcare's history? What need was the company looking to fill in the marketplace?***

Mr. Jacobs: Bilcare came into being because of the vision of Mr. Mohan Bhandari. He has a professional background in packaging sciences and was intrigued to see a very rudimentary level of packaging systems being utilized with crucial life-saving drugs. He visualized the challenges culminating into potential business opportunities, which led to the birth of Bilcare in the form of an application center for evaluating the key issues and concerns of packaging systems related to drug products and the development of innovative solutions. He coined the solution as "Pharma Packaging Research," which began the transformation of the packaging of pharmaceuticals from a conventional containment system to the 5th P of the Pharma branding strategy. The vision was to build continual innovations surrounding the potential five Cs, which would assume prime significance in drug products of the future, namely, Counterfeit, Compliance, Communication, Convenience (of use), and Cost. This was apart from the important functional protection, which the packaging needs to provide in order to safeguard the efficacy, safety, and potency of the drug product it encompasses. The rich expertise gained over years of research gave Bilcare the capability of looking into value-added, end-to-end solutions for the global pharma sector. Bilcare went on to integrate its wide expertise with key areas of clinical supplies, clinical research, and formulation research.

Q: ***What makes the company unique?***

Mr. Bhandari: Bilcare has a host of value-added services, products, and technology offerings for the Specialty Pharmaceutical sector, encompassing the entire value chain from drug discovery to market. Key services include end-to-end clinical supplies management involving the manufacturing, packaging, and

distribution of clinical supplies using multi-location, full-fledged manufacturing centers in key regions of the world. Bilcare becomes the only company in the world to have a manufacturing center for clinical supplies in Asia, with manufacturing and distribution capabilities in the Americas, Europe, and Asia. Other services include formulation development, packaging research and development at all levels of the pharma value chain, and clinical research management services on the Indian continent. Products include a range of specialty films and foils for unit-dosage form packaging of products requiring a variety of specific protection and end-use features. The technologies include use of novel patented technologies, which encompass the integration of IT and electronic-enabled technologies as well as novel evaluation technologies that are very precise, accurate, and require significantly lower evaluation time in the functional defining of a viable packaging system for any product.

Q: ***What needs do Specialty Pharma customers typically have that bring them to Bilcare?***

Mr. Bhandari: Pharma customers today are increasingly besieged with multiple issues and concerns for their global brands, like counterfeiting and branding strategies. Counterfeiting of drug products has become more lucrative than the counterfeiting of currency because it is very easy to do and the product is consumed, leaving no proof. Functional efficacy of the product through its entire shelf-life and across all climatic zones is also a key challenge. Cost becomes challenging when the product needs to be in a singular system and available across the globe. Limitations in innovations that could enhance compliance are becoming critical. Branding strategies that use packaging as a key differentiator are becoming more essential. All of these needs drive pharma customers to Bilcare, which has in its years of research developed a range of innovative solutions addressing specific and multiple issues.

Q: ***As a CRO, what is the key to a successful clinical trial and research program? What is the biggest mistake companies make during this time?***

Mr. Jacobs: The key to success and management begins with great project planning. Next, it is crucial to partner with a great clinical service provider to fill any gaps that may exist within the program at the time. The biggest mistake most companies make is not providing enough time in the project plan for the formulation, stability, packaging, and regulatory review that are required to provide what is necessary for the clinical trial.

Mr. Bhandari: Bilcare, with its comprehensive clinical supplies management capabilities worldwide, has the ability to support any global clinical trial with local management. This leads to significant cycle time reduction in the initiation of trials in specific regions, giving a tremendous capability to the innovator in bringing its valuable discovery to the market at significantly enhanced speeds. Our turnover time has been significantly faster due to the capability of providing supplies management right at the doorstep in any of the key regions for a global trial. Apart from global supplies management capabilities, our clinical research management capability on the Indian continent gives a sponsor the much-needed flexibility of a single source for the effective initiation and completion of trials with best-in-class GMP and GCP. Clinical trials also need much more critical understanding of the total functionality of the product through the entire trial process. Integrating our expertise in the design and development of the most suitable system ensures that the product under trial does not functionally deteriorate throughout the trial period.

Q: ***It seems that Bilcare considers packaging research a core competency. Can you describe where you make the biggest difference for customers in this aspect?***

Mr. Bhandari: The innovations of a pharma company get converted into dosage forms that are as conventional as they were decades ago for the consumer. What the consumer needs to appreciate is the novelty of the research drug that he is consuming. The end user could get these communications from the packaging that holds the novel drug. Research surveys have aptly justified the importance and value of a packaging system in not only communicating to the end-user but in addressing all the key issues and concerns the pharma sector is facing today and will face in the future. These dynamic concerns are what Bilcare has been able to address very effectively through its core expertise in materials, and the company has been successful in creating many critical successes for several drug products in the market.

Q: ***Can you share with our readers some of the drugs that you helped bring to market?***

Mr. Jacobs: I wish I could, but that is confidential to our business partners and customers.

Mr. Bhandari: With regard to existing products on the market, there are many cases where we have been able to create new solutions that have led to the significant enhancement of the market share of these products.

Q: ***Are there certain types of delivery methods you focus on?***

Mr. Jacobs: We can handle solid, semi-solid, and liquid products. We can also manage sterile products as long as they are already in their primary containers.

Q: ***How do you envision the future of CRO services in Specialty Pharma in the next 5 to 10 years?***

Mr. Jacobs: The pharma and biotech industries are growing. CRO services will have to grow with them and will need to become more partner oriented rather than customer oriented. They will act more to help their industry partners avoid missteps and delays and will be more involved in various steps of the development process in which the CROs' expertise and speed to execute will be an excellent complement to the companies that hire them.

Mr. Bhandari: Also, the need of naive patient populations encompassing all ethnic diversities will make these services spread across the globe. This would result in the need to significantly upgrade the level of GCPs in regions across the world to the levels of regulated markets like the US, Europe, and Japan. CRO services will no longer be concentrated in specific regions and will spread globally.

Q: ***What are your long-term goals for the company?***

Mr. Bhandari: Our long-term goal is to be the premier, end-to end solution provider to the global pharma sector. We can meet all the critical needs in their value chain from drug discovery to market, and can partner with the sector to bring their value innovations to market by integrating our solutions and technologies to produce novel products that are complete in all respects.

Q: ***What are your thoughts on what will spur and stifle the Specialty Pharma industry in the next 5 to 10 years?***

Mr. Jacobs: What will spur the industry is the growing innovation and entrepreneurship in the Specialty Pharma sector. What could stifle it is the philosophy of immediate returns on investment from a compound that could take a little while to show its value and how it can benefit worldwide healthcare.

Mr. Bhandari: The need for value-based innovations with globalization, and the associated challenges arising from these, will continue to drive the industry in the next decade. The inability to integrate evolving solutions may lead to a lack of focuses and stagnant growth.

Q: ***Is there one message you want to get across to Specialty Pharma's readers?***

Mr. Jacobs: We want to work with people who we can help to bring great pharmaceutical or biotech compounds to market. If you are looking for excellent project management for your clinical supplies and services, and highly motivated and experienced people, we are the company for you.

Mr. Bhandari: Bilcare has dedicated itself to the pharma sector. People are the core strength of the organization, and the focused commitment of the company motivates our people. This makes our employees go that extra mile to spread excellence across the globe. ■

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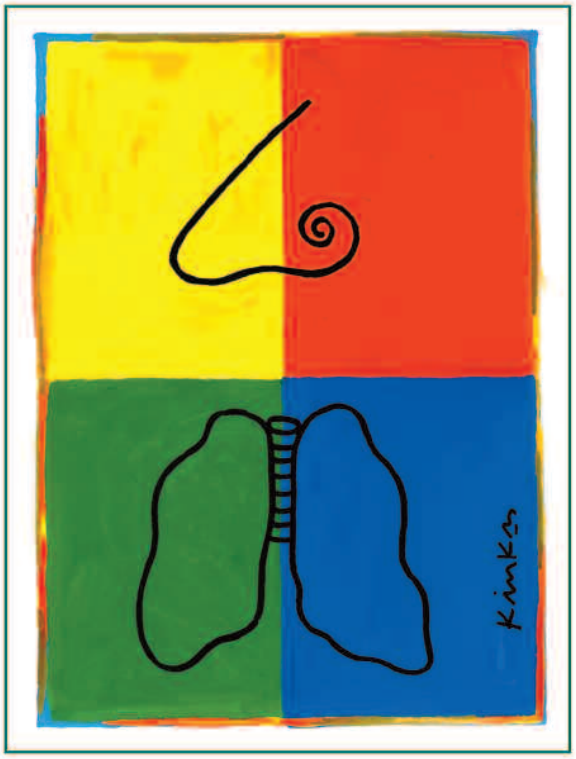

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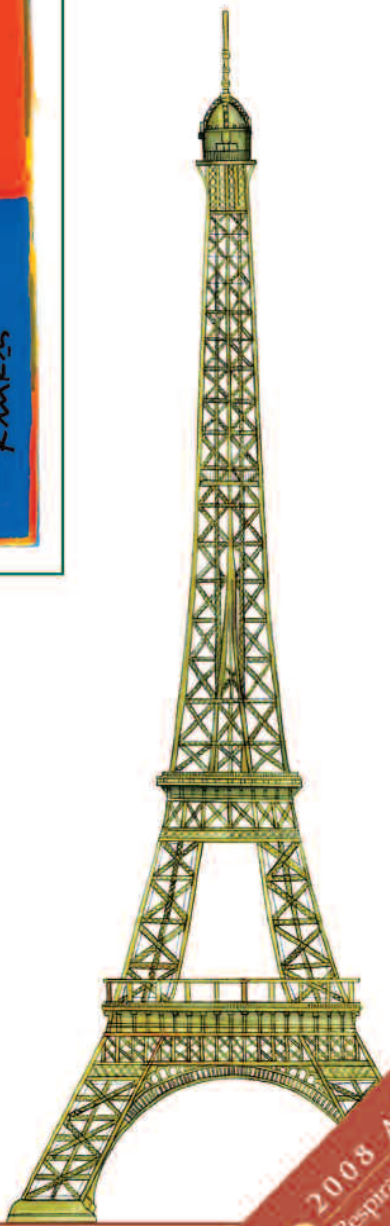

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Technology Showcase

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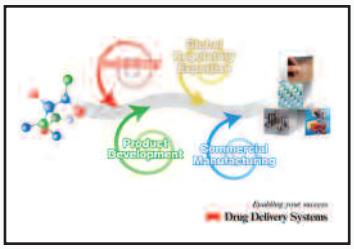

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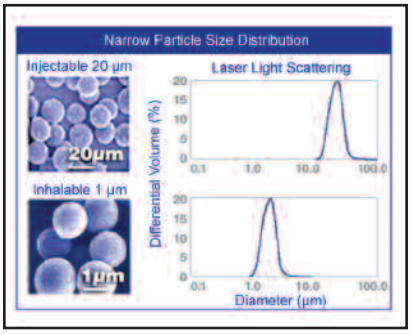

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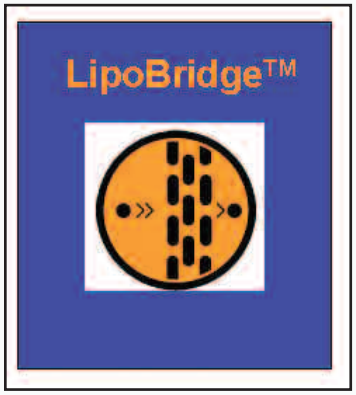
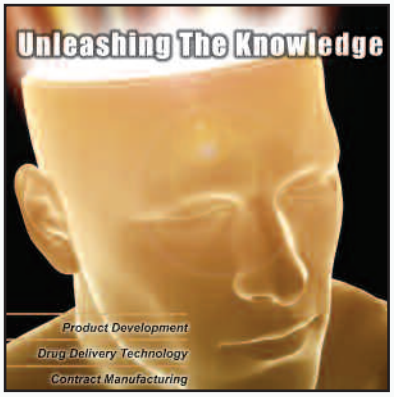


Lipobridge™ compounds facilitate transport of drugs across the blood-brain-barrier (BBB) and into the CNS. Short chain oligoglycerolipids have been shown to facilitate the delivery, distribution, and uptake of pharmaceutical actives into the CNS and thereby permeate the BBB. Data shows that some of these molecules can increase drug concentration reaching the CNS by a factor up to 100 without toxic side effects. Demonstrated in several laboratories, intracarotic injections of a simple mixture of Lipobridge and model compounds or pharmaceutical actives can be delivered into one or both hemispheres of the brain allowing for increased concentration in a selected hemisphere. This permeability has been shown to be reversible and has been demonstrated that the carrier itself is excreted unmetabolized. For more information, contact Genzyme Pharmaceuticals at (800) 868-8208 or visit **www.genzymepharmaceuticals.com.**

Pharma Development Services



It is critical for a service provider to meet the technical, financial, and timing demands of projects and offer clients first-class expertise and capabilities throughout the world. The Glatt Group has been supplying solid dosage technology, equipment, integrated systems, and processing expertise to the global pharmaceutical industry for the past 50 years along with the highest level of support and commitment possible. Glatt uses this extensive experience to provide solutions to partners from the initial concepts in product and formulation development through process scale-up to commercial manufacturing of solid dosage products. With facilities in New Jersey, Germany, and Switzerland, Glatt is uniquely positioned to apply its considerable solid dosage development and manufacturing assets to major markets within the industry. For more information, contact Glatt Pharmaceutical Services at (201) 825-8700 or visit **www.glattpharmaceuticals.com**.

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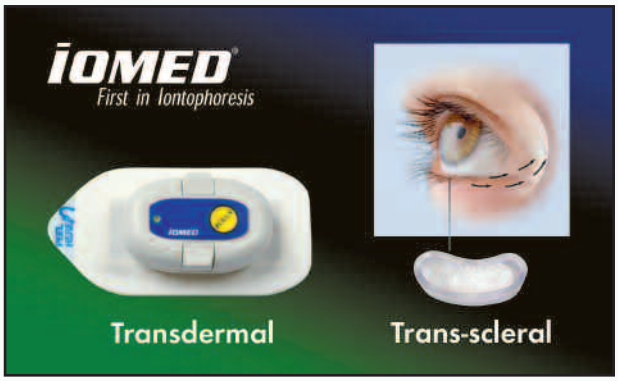

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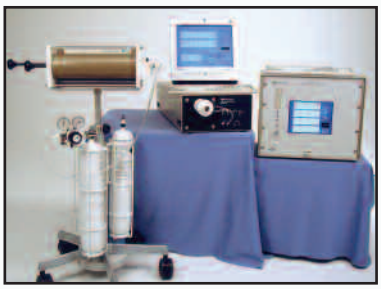

Hans Rudolph, inc. (makers of respiratory products since 1938) manufactures three Lung Simulators. The DLco Simulator with EasyLab QC™ Software is used by pulmonary labs performing drug studies. This patented device & software allow the quality control & testing of the respiratory devices that measure the diffusion lung capacity of patients during drug delivery trials and specifically the new non-invasive inhaled insulin technologies now available. Also available is a Flow/Volume Simulator for R&D, testing, and calibrations on aerosol devices, peak flow meters, spirometers, and other devices requiring the generation of the ATS and custom breathing waveforms. A spontaneously breathing lung model - the Breathing Simulator - is made for R&D, testing, training, and calibration of ventilators, CPAP blower devices, and other respiratory therapy devices. Demonstrations available at Hans Rudolph's booth # 1713 - ATS (American Thoracic Society) Show in San Francisco this May 20-22, 2007. Contact Hans Rudolph at (800) 456-6695 or (816) 363-5522; email: hri@rudolphkc.com; or visit **www.rudolphkc.com**.

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Technology Showcase

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Technology Showcase

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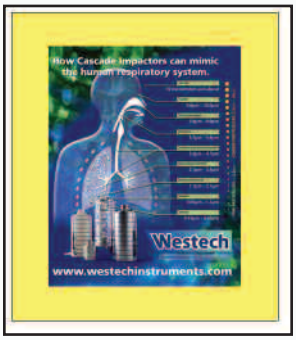

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Who's Mr. Stupid?

By: John A. Bermingham

I have decided that Dennis Kozlowski, the former Tyco CEO who is now serving 8 to 25 years in a Federal lock-up in upstate New York, must think that all of us are really stupid.

Last night, I watched 60 Minutes with great fascination as Morley Safer interviewed Mr. Kozlowski from his prison. In Kozlowski's opening comments, he stated that he still believed in the judicial system but that, in his case, the jury got it wrong. He went on to say, "I was a guy sitting in a courtroom who made $100 million a year. And I think that a juror sitting there just would have to say, 'All that money? He must have done something wrong.' I think...it's as simple as that."

Well, that jury believed there was enough evidence to convict him of 22 counts of grand larceny, conspiracy, and securities fraud. I found it interesting that Morley Safer stated that Kozlowski made $170 million in 1 year to which Mr. Kozlowski answered, "I'm not sure $170, but I made over $100 million."

Then he goes out and has Tyco buy he and his wife a $19-million apartment in New York and decorated it with $11 million worth of stuff also at Tyco's expense. Remember the $6,000 shower curtain?

What about his own money? He made over $100 million in 1 year so he says.

But the best was the $2-million dollar 40th birthday party for his wife. Because he claimed it was a work retreat, he had Tyco pick up $1 million of the cost. Some work retreat if you saw the tape of the party. Does the word toga jog your memory?

Mr. Kozlowski still maintains his innocence stating that, "I am absolutely not guilty of the charges brought upon me." Uh, right!

Now, we all work hard and earn a living, and we know there are certain rules of conduct that all people have to follow in their companies. Even CEOs! I believe the problem here is that too many successful CEOs read their own press releases too closely and become pompous, arrogant, egomaniacs and are above everyone else. That said, they believe they can do whatever they want to include wasting shareholder money for their own benefit. Uh, make that stealing shareholder money!

SO it really is a situation in which CEOs like Mr. Kozlowski believe the ruler of acceptable company conduct and personal ethics are for others, not themselves. Or is it, as my wife thinks, that people like this believe they will never be caught. Regardless, CEOs are responsible for their conduct and must set the right example for everyone. Leadership is leadership, and the CEO is responsible for setting the right example.

So let me make one other point here. Where was the Board of Directors when Mr. Kozlowski was running through shareholder money? How could they allow half of the expense of the $2-million birthday party for Mr. Kozlowski's wife to be charged to the company, not to mention the "bazillion" dollar apartment in New York? Perhaps they were part of the toga crowd at the birthday party. I just don't get it. ◆

Biography

John A. Bermingham is currently the CEO of The Lang Companies, an innovative leader in the social sentiment and home décor industries. He was previously the President, Chairman, and CEO during the successful turnaround and sale of Ampad, a leading manufacturer and distributor of office products. With more than 20 years of experience in guiding enterprises to new levels of performance, Mr. Bermingham also held the positions of Chairman, President, and CEO of Centis, Inc., a diverse multinational manufacturer and marketer of office, storage, and human resources products. Among many career highlights in the role of President and CEO, he also successfully reorganized Smith Corona Corporation and refocused operations and a strategic vision for a dramatic turnaround for Rolodex Corporation. Mr. Bermingham's expertise has also been deployed at industry giants, such as AT&T Consumer Products Group, and by having served as the EVP of the Electronics Group and President of the Magnetic Products Group, Sony Corporation of America. Mr. Bermingham served three years 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.

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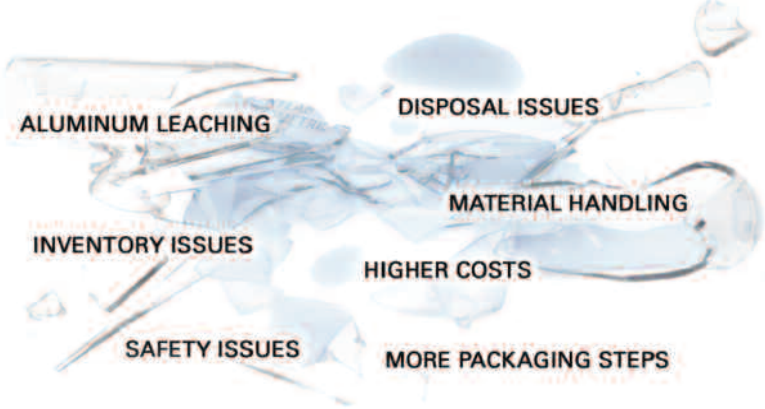

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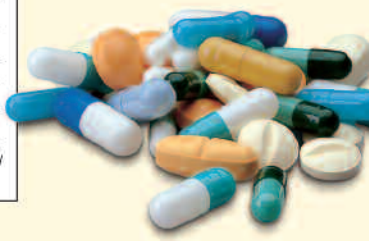

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