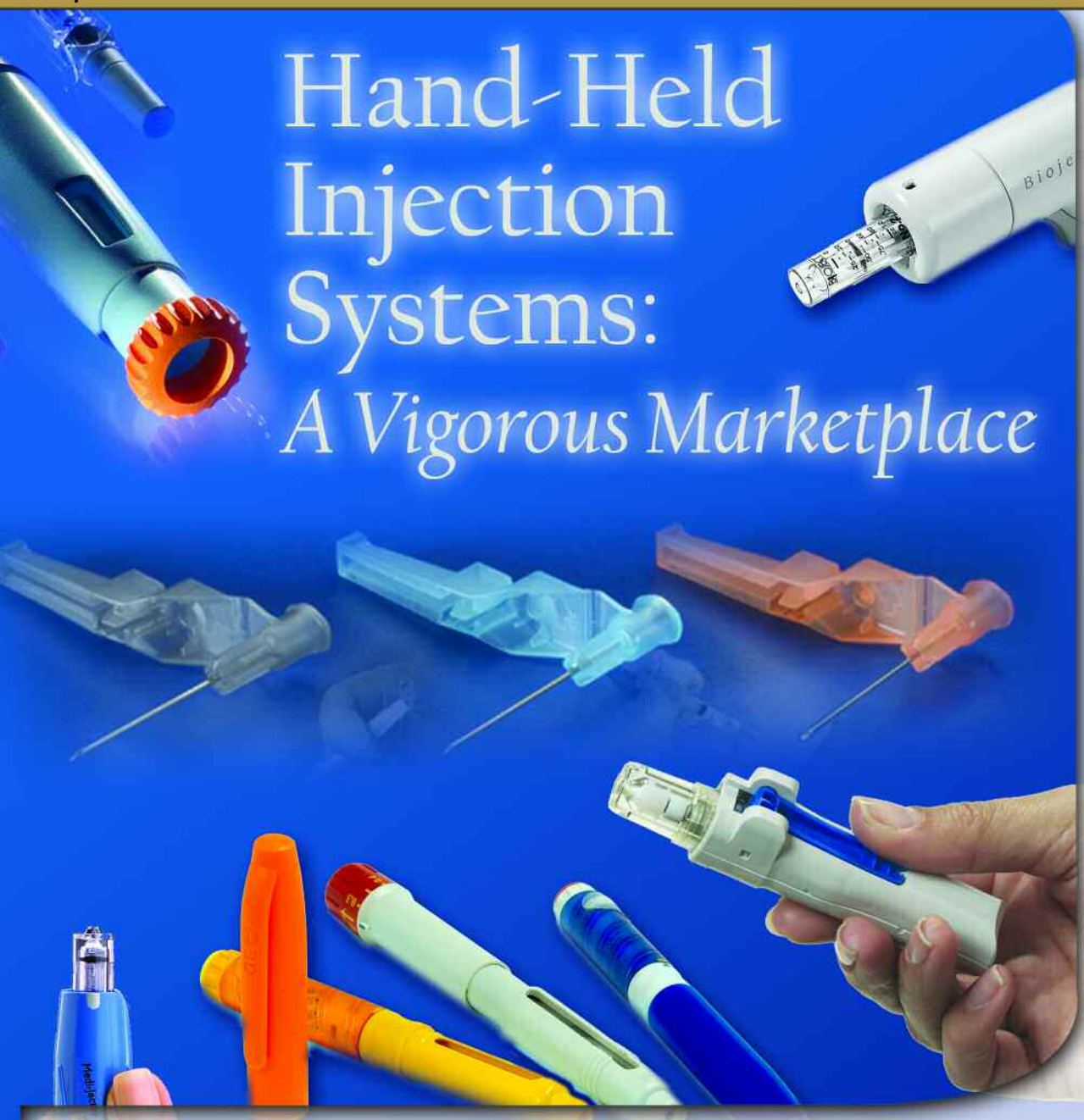
Drug Delivery Technology®

September 2006 Vol 6 No 8

Hand-Held Injection Systems: A Vigorous Marketplace



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

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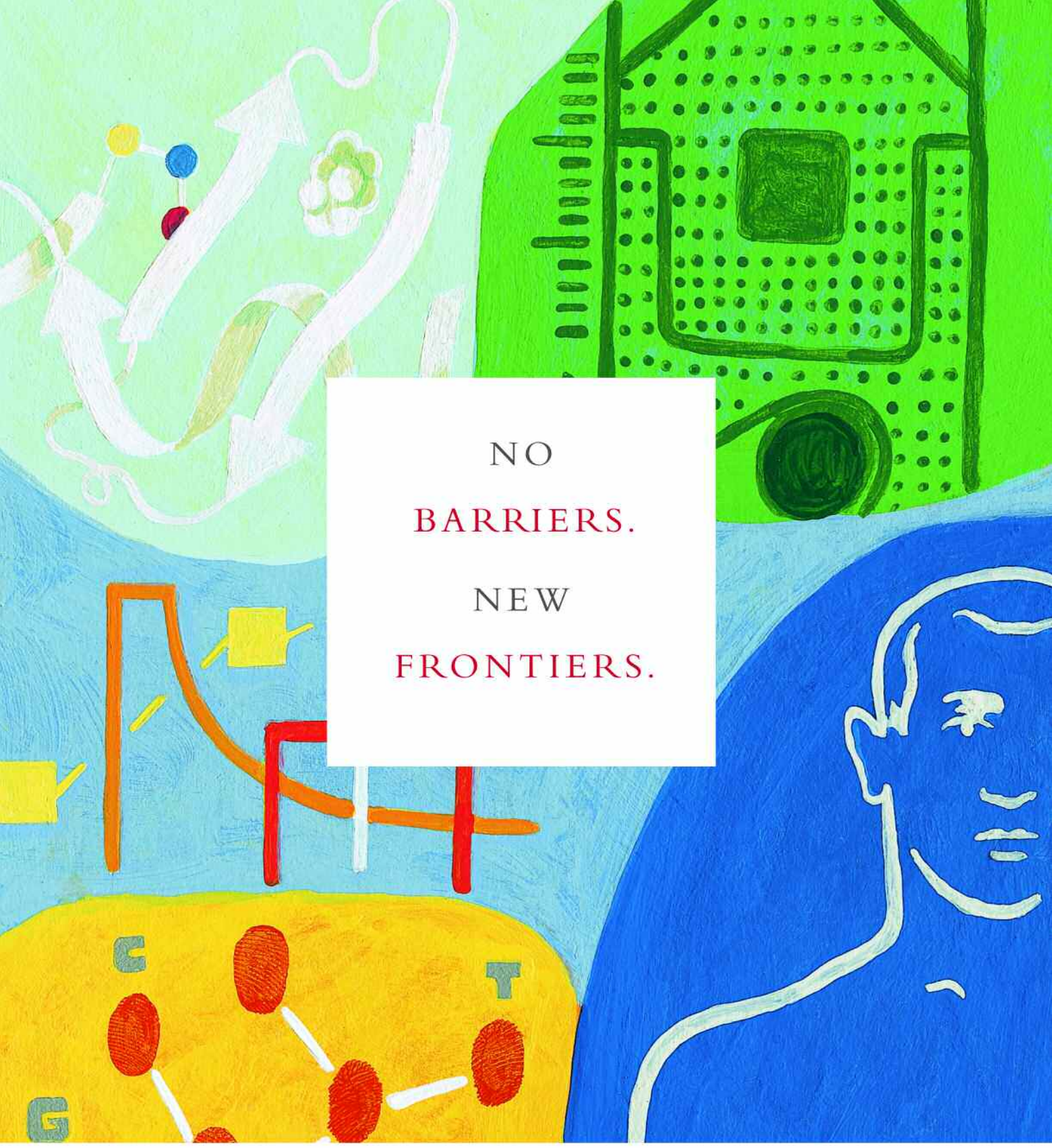

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Hand-Held Injection

"While advanced drug delivery techniques continue to hold promise for unique methods of administration, the traditional injection is still the dominant paradigm. However, the staggering costs and intransigent safety problems associated with sharps, along with consumer demand and the move to alternate-site care, are pushing for alternatives to traditional needles (needle-free or needle-based) and syringes faster than advanced delivery technologies can come online."

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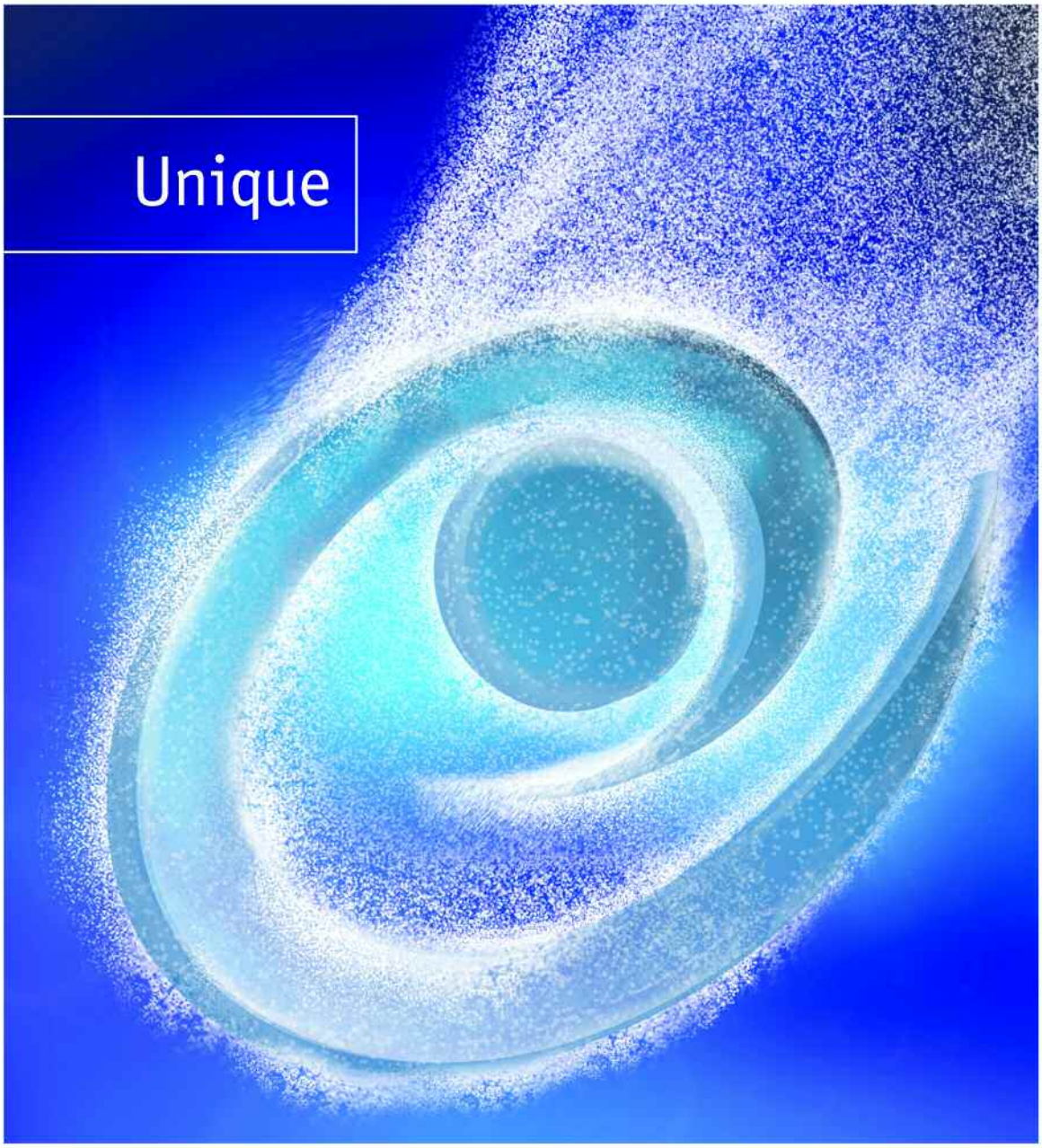

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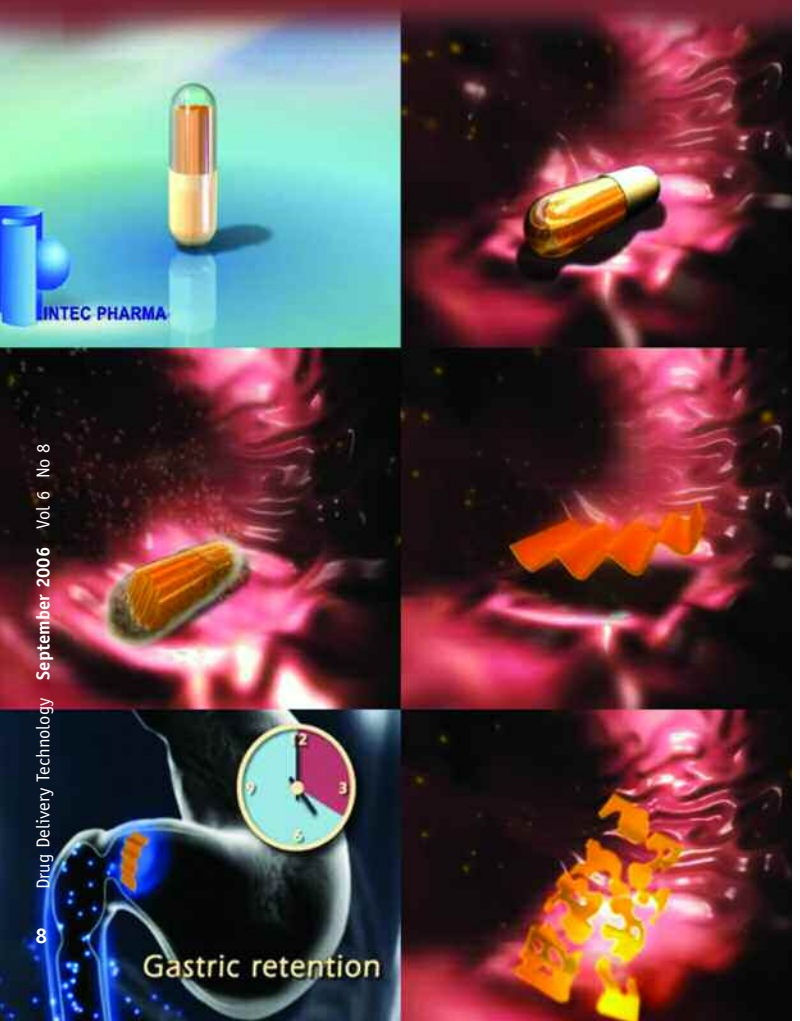
p.46



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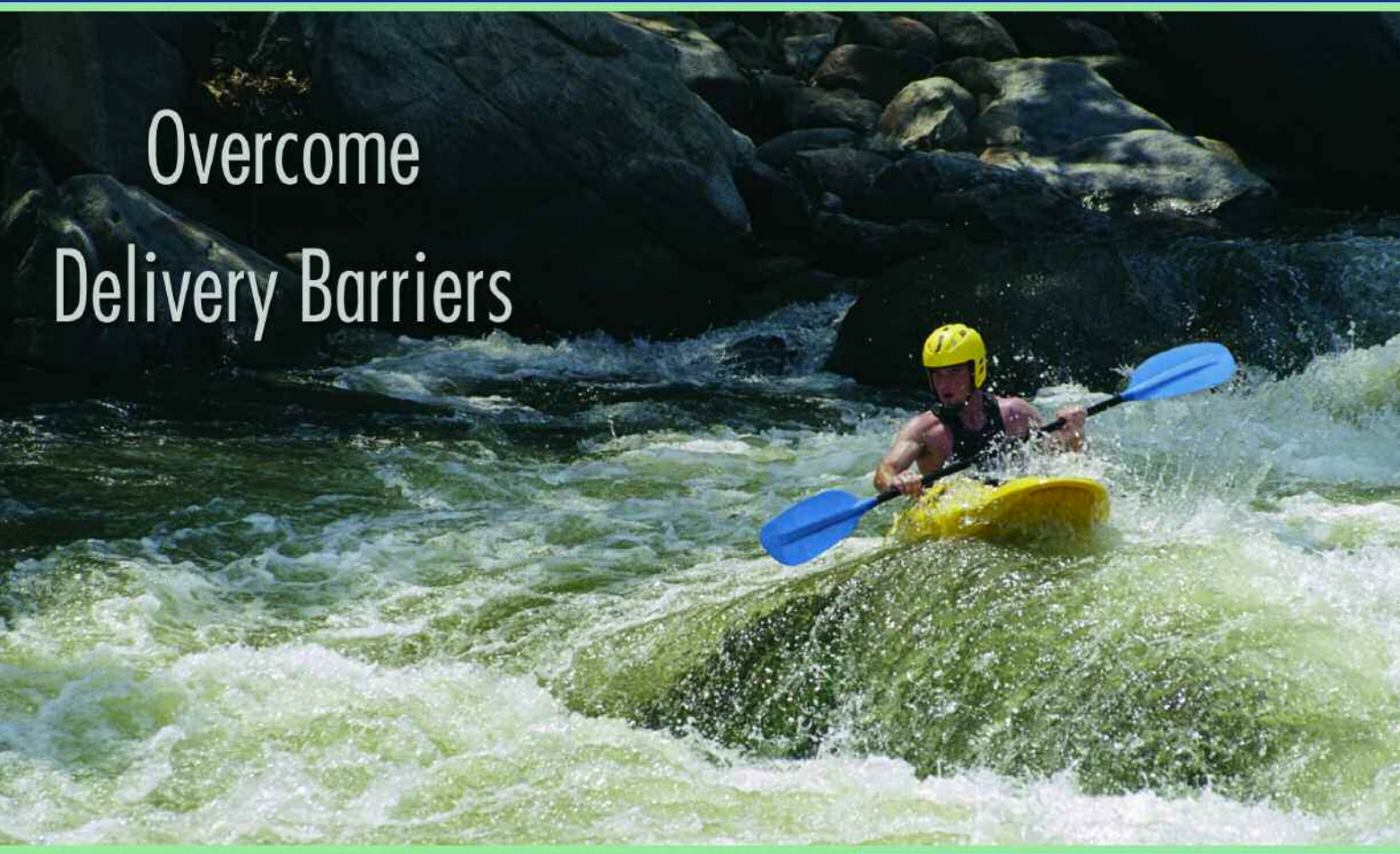

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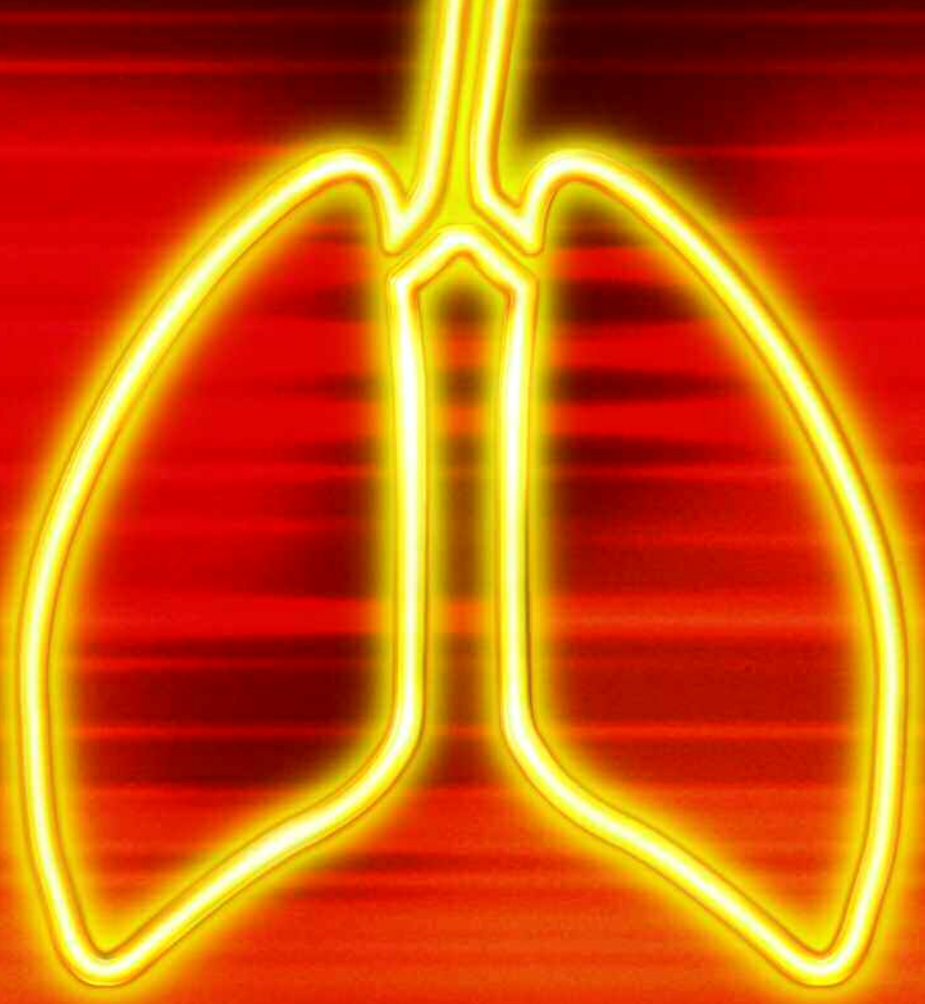

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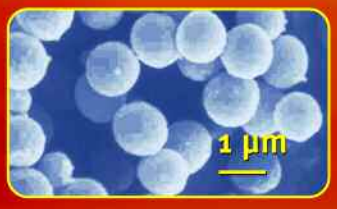

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Market News and Trends

TransPharma Medical Completes $18 Million Series C Financing

TransPharma Medical Ltd., a specialty pharmaceutical company focused on the development and commercialization of drug products utilizing a proprietary active transdermal drug delivery technology, recently announced it has secured $18 million in Series C financing. This oversubscribed Series C funding round was led by Argonaut Private Equity and includes an additional new investor, Teva Pharmaceutical Industries Ltd., as well as TransPharma's current investors: Pitango Venture Capital, Evergreen Partners, T2C2/Bio, Vitalife, Biomedical Investments, and TIF Ventures Pte Ltd. As a result of the financing, Jason Martin, Managing Director of Argonaut will join the company's board.

TransPharma will use the funds to progress its lead project, transdermal hPTH (1-34), into advanced clinical trials. Earlier this year, the company announced promising human clinical results demonstrating efficient and effective transdermal delivery of hPTH (1-34) for the treatment of osteoporosis. TransPharma plans to continue its development process in-house, bringing this high-potential product to an advanced clinical stage before seeking a partner to take it to market.

The company also plans on using the funds to initiate development of additional drug products in 2007, as well as develop a new generation of transdermal drug delivery systems and scale-up production of its current ViaDerm delivery system.

"TransPharma's accomplishments during the 6 years since its inception are impressive, having succeeded in developing an innovative technology and bringing its drug products to clinical trials in a short amount of time," said Jason Martin, Managing Director, Argonaut Private Equity. "With its strong management team, unique active transdermal delivery system, and substantial market potential for its product pipeline, we believe TransPharma is well positioned as a leader in the drug delivery field."

"We are delighted to have concluded this financing round with a syndicate of highly accomplished investors, and are particularly pleased to be adding two new remarkable investors – Argonaut, a diverse private equity fund with unique financial vision, and Teva, a global pharmaceutical company that has already proven to be a productive and valuable partner for us," said Dr. Daphna Heffetz, Chief Executive Officer of TransPharma Medical Ltd. "With the support of our new and existing investors, we will continue to advance our drug products into further stages of development while expanding our product pipeline to include additional drug products."

TransPharma currently has a joint development agreement with Teva for up to five molecules. The company has already successfully completed initial clinical trials on the first of these molecules. Under the agreement, Teva will exclusively market each of the drug-products and will pay TransPharma milestone payments, royalties, and development costs.

"We are very impressed by the quality and productivity of TransPharma's team thus far in our joint development agreement, which produced successful initial clinical results earlier this year," said Dr. Aharon Schwartz, Vice President, Strategic Business Planning and New Ventures, Teva Pharmaceutical Industries. In the coming years, TransPharma will continue working closely with Teva on the development of the specified molecules, as well as planning to ally with other companies for developing additional drug products."

Nektar Announces Receipt of $17.6 Million Payment From Affymax Under Agreement for Nektar Advanced PEGylation Technology

Nektar Therapeutics recently announced it has received a $17.6 million payment under a previously undisclosed license agreement with Affymax, Inc. The cash payment under the Nektar-Affymax agreement was triggered by Affymax entering into a global agreement with Takeda, Inc. to develop and commercialize Affymax's lead product candidate, HematideTM. Hematide utilizes Nektar Advanced PEGylation Technology and is in Phase IIb clinical trials for the treatment of anemia.

Nektar and Affymax entered into a partnership in 2004 under which Nektar provides Affymax with its Advanced PEGylation Technology to develop Hematide. Under the terms of the agreement, Nektar receives manufacturing revenue, milestone, and other payments, as well as royalties on worldwide end-product sales. Nektar first announced the agreement in May 2004 as a collaboration with an undisclosed biotechnology company.

"This payment highlights the value of Nektar PEGylation technology, which is used in eight marketed products and two additional products filed for regulatory approval in the US and Europe," said Rob Chess, Nektar Chairman and acting Chief Executive Officer and President. "Our PEGylation technology has proven its ability to create blockbuster drugs for our partners. As part of our focus on expanding our PEGylation business, Nektar is identifying and developing our own proprietary products using PEGylation. This includes two early-stage programs in our pipeline in the disease areas of oncology and pain."

Nektar Advanced PEGylation has the potential to improve the safety and efficacy of therapeutic agents by increasing drug circulation time in the bloodstream, decreasing immunogenicity and dosing frequency, increasing bioavailability, and improving drug solubility and stability. It is based on the use of non-toxic polyethylene glycol (PEG) polymers, which can be attached to most major drug classes, including proteins, peptides, antibody fragments, small molecules, and other drugs and is used in eight approved products in the US and/or Europe today. Two other products using Nektar Advanced PEGylation have been filed for approval by Nektar partners in both the US and the European Union, including UCB's CimziaTM for Crohn's Disease.

Hematide, a synthetic, peptide-based erythropoiesis-stimulating agent (ESA), is designed to stimulate the production of red blood cells. The product is in Phase IIb clinical trials for anemia in dialysis, pre-dialysis, and cancer chemotherapy patients. ESAs address currently a $12 billion market worldwide and have been used successfully to manage anemia in patients with chronic kidney disease (CKD) and cancer-related anemia. They reduce the need for blood transfusions and the frequency and severity of anemia-associated morbidity, resulting in an improved quality of life for patients.

Nektar Therapeutics is a biopharmaceutical company that develops and enables differentiated therapeutics with its industry-leading drug delivery technologies, expertise, and manufacturing capabilities. Nektar technology and know-how have enabled nine approved products for partners, which include the world's leading pharmaceutical and biotechnology companies. Nektar also develops its own products by applying its drug delivery technologies and expertise to existing medicines to enhance performance, such as improving efficacy, safety, and compliance.

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Market News and Trends

Auriga Announces New Alliance With Degussa

Auriga Laboratories, Inc. recently announced the execution of a strategic agreement with Degussa to develop a proprietary formulation targeting serious chronic gastrointestinal diseases utilizing Degussa's proprietary EUDRACOL technology. Auriga is developing an oral, controlled-release corticosteroid formulation that targets inflammatory bowel disease lesions at different sites within the GI tract. Degussa, the world's largest specialty chemical company, will provide the proprietary drug delivery technology and formulation concentrating the therapeutic benefits of the selected corticosteroid specifically where it is needed in the GI tract, providing dosing and efficacy, and reducing side effects. Drug delivery to specific disease sites within the GI tract is essential for the creation of improved pharmacological treatments with greater efficacy and reduced side effects for the patient suffering from Inflammatory Bowel Diseases. By joining forces with Degussa now to develop this novel formulation with targeted delivery, and in combination with Auriga's existing development pipeline, Auriga establishes itself as a valued development partner in the specialty pharmaceutical marketplace. Under the terms of the development agreement, Degussa is responsible for development of the prototype formulations. Auriga Laboratories is responsible for formulation scale-up, manufacture, clinical, regulatory submission/approval, and product launch and marketing. EUDRACOL is a proprietary multi-layer colonic drug delivery system that is designed to provide drug protection in the upper gastrointestinal tract and controlled drug release in the ileum and colon.

Aradigm & Novo Nordisk Execute Further Restructuring of Partnership; Agreement Raises $27.5 Million & Facilitates Advancement of Proprietary Programs

Aradigm Corporation recently announced the execution of an agreement further developing the strategic partnership with Novo Nordisk. The agreement is designed to strengthen Novo Nordisk's patent position within the area of inhaled insulin as related products progress toward commercialization and has resulted in a non-dilutive cash infusion to Aradigm of $27.5 million. The Novo Nordisk inhaled insulin program is currently in Phase III clinical trials. This agreement is composed of an intellectual property assignment, a royalty prepayment, and an 8-year promissory note. The promissory note is secured by the royalty payments on the AERx Diabetes Management System (iDMS) sold under the Aradigm license.

The key features to the restructuring and cash infusion include Aradigm's receipt of $12 million in exchange for transferring to Novo Nordisk the ownership of a select number of patents that are especially important for inhaled insulin. Aradigm will retain exclusive, royalty-free control of these patents outside the field of glucose control and will continue to be entitled to royalties in respect to any inhaled insulin products marketed by Novo Nordisk. The receipt by Aradigm of $8 million in exchange for a 100 basis point or 1% reduction on its average royalty rate set forth by the commercialized AERx iDMS product. This will result in Aradigm receiving royalty rates that will rise to an average of 5% or higher by the fifth year after commercialization. Finally, Novo Nordisk has paid Aradigm $7.5 million in a 5%, 8-year note that is payable in three equal payments commencing in 6 years, and is secured by the royalty payments to Aradigm upon the commercialization of the AERx iDMS product.

"We appreciate and are impressed by the significant and increased commitment by Novo Nordisk to both the AERx technology and bringing the AERx iDMS to market in the fight to manage the growing diabetes epidemic," said Dr. Bryan Lawlis, Aradigm's Chief Executive Officer. "Together with this cash infusion, Aradigm now has more than $35 million in cash, which will advance our AERx respiratory focused programs, including our self-initiated liposomal ciprofloxacin program for the treatment of cystic fibrosis-related infections. Going forward, it is our intent to balance both partnered and self-initiated AERx opportunities with the goal of full ownership of products in the future."

Aradigm combines its non-invasive delivery systems with novel formulations to create products that enable patients to comfortably self-administer biopharmaceuticals and small molecule drugs. The company's advanced AERx pulmonary and Intraject needle-free delivery technologies offer rapid delivery solutions for liquid drug formulations. Current development programs and priorities focus on the development of specific products, including partnered and self-initiated programs in the areas of respiratory conditions, neurological disorders, heart disorders, and smoking cessation. In addition, Aradigm and its partner, Novo Nordisk, are in Phase III clinical trials of the AERx Diabetes Management System for the treatment of type 1 and type 2 diabetes.

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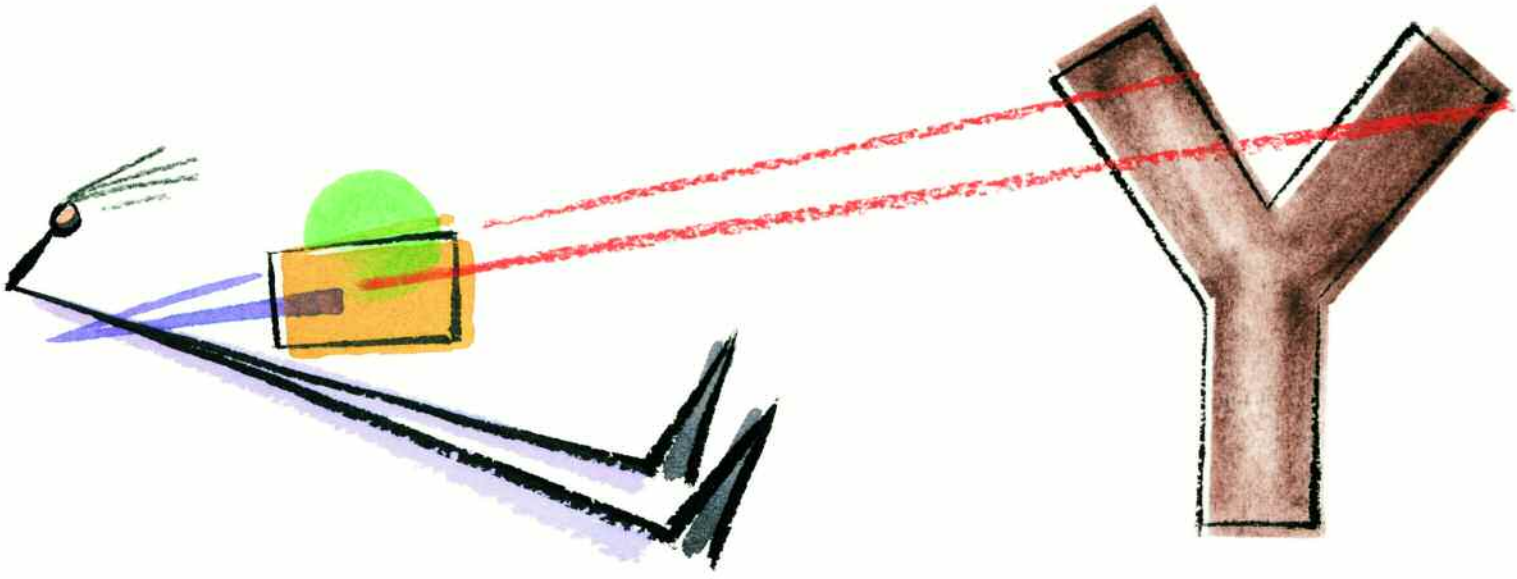

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Market News and Trends

Nostrum Pharmaceuticals Obtains Worldwide Licensing Rights From IMTECH for Clinical Development of Novel Clot-Busting Therapeutic Protein

Nostrum Pharmaceuticals, Inc., a privately held company based in Kendall Park, New Jersey, recently announced it has obtained a worldwide license from the Institute of Microbial Technology (IMTECH), Chandigarh, India, to carry out clinical development and commercialization of a novel clot-busting therapeutic protein.

Nostrum will develop this therapeutic protein in association with Symmetrix Pharmaceuticals, Inc., an affiliate of Nostrum Pharmaceuticals. Symmetrix Pharmaceuticals, Inc., a biopharmaceutical company also based in New Jersey, was founded by Dr. Yatindra Prashar, who is a renowned biotechnologist. Dr. Prashar was scientific Co-Founder of Gene Logic, Inc., a Gaithersburg, Maryland-based biotechnology company.

IMTECH, which is one of the premier institutes governed by the Council of Scientific and Industrial Research (CSIR), Government of India, is a premier biology research institute in India focusing on emerging areas of biotechnology and microbiology. With more than 100 PhD students and several post-doctoral scholars, it is one of the best funded and highly reputed biotechnology research institutes in India that has an enviable infrastructure consisting of a wide array of the latest, state-of-the-art equipment and instruments required for biotechnology and microbiology research.

The therapeutic protein being licensed by Nostrum is known as Clot Specific Streptokinase (CSSK), which was developed at IMTECH by Dr. Girish Sahni, Director of the institute. CSSK is an engineered protein produced by recombinant DNA technology. The cDNA coding for streptokinase has been fused with the cDNA of another naturally occurring human blood protein. The resulting hybrid protein is a product that has a very high affinity for the blood clot, while it does not have any plasminogen lysis property. However, upon binding to the blood clot protein fibrin, the hybrid protein is lysed into its individual component proteins. As a result, streptokinase is released and is active only in the vicinity of the blood clot. Therefore, the common problem of blood thinning associated with streptokinase due to general and widespread plasminogen lysis in the blood that can cause severe bleeding and hence death in some cases will be avoided when CSSK is used. IMTECH has obtained a European patent for this molecule, and the Indian and US patents are pending.

"Development of CSSK is the result of remarkably ingenuous protein engineering research at IMTECH, and we are very excited about taking this therapeutic protein into clinical development because CSSK works in a highly clot-specific manner and hence overcomes the major problem of blood thinning that is otherwise associated with streptokinase," said Dr. Nirmal Mulye, President and Founder of Nostrum Pharmaceuticals. He further added, "We are excited and honored to have this relationship with one of the premier research institutes in India with a large pool of highly talented scientists lead by Dr. Sahni."

Dr. Girish Sahni, Director IMTECH, said "Nostrum, a technology-driven company, has the focus and agility of a small company, and access to intellectual and financial resources to pursue clinical development of a molecule that has a huge commercial potential in the market worldwide. We are highly impressed with these talented scientists turned entrepreneurs, Dr. Mulye and Dr. Prashar, who recognize the potential of this invention and are capable of spearheading the international development of a molecule of such commercial and medical importance."

Mr. Kapil Sibbal, Minister of Science and Technology, Government of India, while speaking on the occasion, expressed his happiness on this tie-up and opined that such agreements on new and improved drugs signal the coming of age of India's scientific and technological capabilities. The Honorable Minister noted that the research being carried out by many of the R&D institutions are now coming at par with those from globally recognized companies. Mr. Sibbal observed that IMTECH is one such example of having world class creative ambience, which is reflective in its achievements, such as clot-specific streptokinase.

Mr. Sibbal was particular happy to note that this tie-up represents a "brain gain" for India. Both Dr. Nirmal Mulye and Dr. Yatinder Prashar are India born American citizens who, Mr. Sibbal noted, exude a strong love and desire to serve their motherland. He termed it as a happy augury and hoped many more such tie-ups would follow.

Dr. Raghunath Mashelkar, the Director General, India's Council of Scientific and Industrial Research, complimented all the scientists and technical staff engaged in development of this technology which is indeed a cutting-edge one. According to him, it represents a paradigm change in the working of government sector Indian R&D labs from primary basic research driven programs to the ones which can be commercially exciting as well. He expressed his confidence that like earlier successful developments of clot blusters, this too would be a huge success for IMTECH.

Nostrum Pharmaceuticals is involved in the development and commercialization of products using novel drug delivery systems for generic and branded pharmaceuticals in the US. Nostrum has recently acquired a large stake in a public company, Synovics Pharmaceuticals, Inc., through which it plans to commercialize various pharmaceuticals products.

Wyeth Infant Meningitis Vaccine Available for Delivery With BD Hypak SCF™ Prefill System

BD Medical-Pharmaceutical Systems, a unit of BD (Becton, Dickinson and Co), recently congratulated Wyeth Pharmaceuticals on their recent market launch of a new prefilled delivery system for Prevnar®, a recommended infant vaccine, which will be delivered to patients using the BD Hypak SCF™ prefill system. BD Medical's partnership with Wyeth helps provide a more convenient delivery system for Prevnar.

"This is great news for Wyeth and for families, and we offer sincere congratulations on this recent approval," said Linda Tharby, Vice President and General Manager US, BD Medical – Pharmaceutical Systems. "The availability of Prevnar in combination with the BD Hypak SCF system will make delivery of this vaccine for infants more convenient."

BD Hypak SCF is the preferred medication delivery system by pharmaceutical companies for vaccines and therapeutic drugs. Prefilled BD Hypak SCF minimizes medication errors, ensures optimal aseptic drug delivery, and, as a result, contributes to cost reduction related to care and drug deliveries. BD's prefilled injectables require less "overfill" than standard medication vials, resulting in the ability to vaccinate a larger number of patients with the same amount of vaccine. Additionally, this single-use system eliminates the need for preservatives to maintain product sterility.

Prevnar helps to protect infants and toddlers from certain pneumococcal bacteria that can cause life-threatening meningitis and blood infections. Prevnar is approved for use in infants as part of their routine vaccination schedule. Prevnar was approved by the FDA in February 2000, but has been available only in single-dose vials. Prevnar is now available in prefilled syringes, the exclusive delivery system.

BD, a leading global medical technology company that makes and sells medical devices, instrumented systems, and reagents, is dedicated to improving people's health throughout the world. BD is focused on improving drug therapy, enhancing the quality and speed of diagnosing infectious diseases, and advancing research and discovery of new drugs and vaccines. The company's capabilities are instrumental in combating many of the world's most pressing diseases. Founded in 1897 and headquartered in Franklin Lakes, New Jersey, BD employs more than 25,000 people in approximately 50 countries throughout the world. The company serves healthcare institutions, life science researchers, clinical laboratories, industry, and the general public.

MARKET NEWS AND TRENDS

BDSI Signs European Licensing Agreement; Announces Purchase of Non-US BEMA Technology

BioDelivery Sciences International, Inc., a specialty biopharmaceutical company focused on acute care products, including pain therapies, and Meda AB, a leading European specialty pharmaceutical company, recently announced a collaboration to develop and commercialize BDSI's flagship BEMATM Fentanyl product in Europe. BEMA Fentanyl is a Phase III product being developed by BDSI for the treatment of breakthrough cancer pain.

Under terms of the agreement, BDSI will grant Meda rights to the European development and commercialization of BEMA Fentanyl in exchange for an upfront fee to BDSI, certain milestone payments, and double-digit royalties to be received by BDSI on product sales. Payments include a $2.5 million payment upon execution of the agreement and additional milestones that would, if achieved, provide BDSI with up to an additional aggregate of $7.5 million in revenue.

Meda will manage the clinical development and regulatory submissions in all of Europe. Upon regulatory approval, Meda will exclusively commercialize BEMA Fentanyl in Europe. BDSI shall retain all development and commercial rights in the US, Japan, Australia, and other territories outside of Europe.

BDSI also announced it has purchased from QLT USA, Inc., a subsidiary of QLT Inc., all of the non-US rights to the BEMA drug delivery technology, including all patent rights and related intellectual property. Prior to this transaction, BDSI had licensed BEMA from QLT USA on a worldwide, exclusive basis. Besides the rights to the BEMA technology outside of the US, the agreement gives BDSI an option to purchase the US BEMA technology patents within 12 months.

The aggregate purchase price for the non-US portion of the BEMA technology is $3 million, to be paid over time as follows: (1) $1 million was paid at closing, (2) $1 million by the end of first quarter 2007, and (3) $1 million to be paid within 30 days of FDA approval of the first non-US BEMA-related product. As part of the transaction as it relates to the non-US portion of the former QLT USA/BDSI license, no further milestone payments or ongoing royalties will be due to QLT USA. In addition, BDSI will have the option to purchase the remaining US asset for $7 million dollars. These payments will also be paid over time.

BEMA is an acronym for Bioerodible Mucoadhesive and consists of a patented oral BEMA disc, which delivers the drug through the mucosal surface by placing the disc between the cheek and gum. BDSI, in its merger with Arius Pharmaceuticals in August 2004, acquired the worldwide license to the BEMA technology and has since been working to develop and commercialize the technology, most notably with its flagship product BEMA Fentanyl, which is now in Phase III for the treatment of breakthrough cancer pain.

Market News and Trends

Bespak is Fully Prepared for Exubera® Launch

Bespak, a leading provider of specialty medical devices, has commenced full-scale production of the Exubera® inhaler in readiness for the imminent US launch of Pfizer's inhaled insulin therapy. Exubera was launched in Germany and Ireland in May 2006.

In conjunction with Nektar Therapeutics, Inc., Bespak has been developing the inhaler's manufacturing process since July 1999. Bespak moulds and assembles more than 450 million complex devices each year, and the company's Milton Keynes facility is almost exclusively geared toward the high-volume production of the Exubera device. Opened in 1998, the state-of-the-art facility provides a 35,000-m2 clean room environment, compliant with all the regulatory requirements necessary to produce delivery devices that come directly into contact with the drug.

Bespak, which has been instrumental in the industrialization of the delivery device, has employed its proprietary planning tool, Bespak Product Introduction Process (BPIP), to deliver the most effective mode of manufacture and ensure the most appropriate utilization of its facilities. BPIP extends beyond the Bespak facility and ensures the quality of components supplied throughout the supply base of more than 20 supplier companies. The manufacturing process at Bespak brings together 30 moulded components to assemble together with 33 bought-in parts and entails a range of processes, including two-shot moulding, ultrasonic welding, cropping, and laser marking.

Mark Throdahl, Chief Executive of Bespak, said "We are delighted that this much anticipated therapy is now almost ready for launch. Our track record in delivering high volumes of complex medical devices means we are fully prepared to meet the substantial demand for this product, and we look forward to participating substantially in the commercial success of Exubera in the coming years."

Exubera is targeted to treat adult patients with types 1 and 2 diabetes. It is estimated that nearly 180 million people worldwide suffer from diabetes, with that number expected to rise to 300 million by 2025. Currently, diabetes and its complications account for healthcare costs of over US $100 billion per year in the US alone.

Bespak, a leader in devices for inhaled drug delivery and anesthesia, develops delivery systems for the pharmaceutical industry and disposable airway management products for critical care settings. Bespak's product range includes metered dose and dry powder inhalers, actuators, inflation valves, breathing circuits, disposable face masks, and laryngeal tubes.

Market News and Trends

Transport Pharmaceuticals Raises $12.6 Million in Venture Financing

Transport Pharmaceuticals, Inc., a leader in drug/medical devices for the topical treatment of dermatological conditions, recently announced the company closed on a $12.6 million extension of its Series D financing round, bringing the total of the round to $29.6 million. This funding comes from existing investors, and was co-led by The Carlyle Group and Quaker BioVentures, with participation by The Hillman Company.

"The continued support from our investors provides further validation of Transport's technology, broad experience in drug development, management team, product focus, and business strategy," said Dennis Goldberg, PhD, President and Chief Operating Officer. "The additional funds will support our lead drug/device combination product for herpes labialis, or cold sores. We will initiate a Phase II human clinical trial to evaluate the effectiveness of our new drug delivery device and proprietary acyclovir formulation. It will also help to advance the preclinical development of the company's onychomycosis and other product candidates."

Richard Kollender, Partner of Quaker BioVentures, added "We continue to be attracted to Transport and its core competencies in electrical engineering, chemistry/drug formulation, materials science and drug development, a new model known as drug/device convergence. Further, Transport's lead product focus in herpes labialis represents a unique market opportunity. This is due, in part, to the ineffectiveness of currently available treatments and the unique drug/device system developed by Transport, whereby acyclovir is delivered over a 10-minute treatment time directly to impacted skin at considerably higher concentrations than existing approved topical formulations."

Transport's drug delivery platform is based on the combination of iontophoresis, a technology employing a low-voltage electrical charge to locally deliver larger amounts of medications through the skin, and proprietary drug formulations optimized for electrokinetic delivery. The company has developed a small, wireless microprocessor-controlled drug delivery device and prefilled drug reservoir cartridges that will allow patients to self-administer topical drugs for a variety of indications. The system consists of a reusable control unit and disposable, single-use medicated cartridges. The prefilled cartridges contain a unit dose of drug.

To date, Transport has clinically validated its iontophoresis technology in several US clinical trials in more than 750 patients using the company's first-generation device and an approved topical acyclovir formulation, including an initial Phase IIb double-blind, placebo-controlled study in which 43% of treated erythema patients reported aborted lesions versus 20% for placebo, a 50-hour improvement in healing time for treated patients versus placebo and a 35-hour improvement in healing time for all patients.

Market News and Trends

Halozyme Initiates First Enhanze Technology Clinical Trial to Improve Subcutaneous Absorption of a Large Molecule Protein Therapeutic

Facet Technologies, a subsidiary of Matria Healthcare, Inc., recently announced an agreement for it to be acquired by a new company formed by Water Street Capital Partners, a Chicago-based private equity firm focused on healthcare. Facet is a leading provider of lancets and lancing devices to the rapidly growing blood glucose monitoring market and in microsampling point-of-care diagnostics.

"Our success comes from innovation, quality, and precision of our lancing-related products," noted Bill Taylor, President of Facet Technologies. "Compliance with routine blood glucose monitoring is essential to effective treatment of diabetes, and we have developed the leading technology that minimizes pain and invasiveness of the needlestick as well as enhancing convenience, – all of which are essential to a positive patient experience."

In addition to being a market leader in the global microsampling sharps market for diabetes testing products, Mr. Taylor added, "We are well positioned to participate in the broader specialty sharps business, including vascular suturing, biopsy, and other specialty surgical devices, where precise manufacturing and innovation in product development is equally essential. Water Street's acquisition of our business and the additional growth resources that they bring offers us the opportunity to further enhance our technologies for the diabetes market. It also allows us to expand into other diagnostic arenas in which fabrication of precise sharp components and related devices is equally critical."

Facet's products serve people with diabetes who must routinely monitor their blood glucose levels as a key element of managing their condition. The company's ability to consistently meet the exacting requirements of blood glucose monitoring technology has established it as a worldwide leading provider of microsampling devices. Diabetes is a fast-growing public health problem, with the incidence of the disease in the US doubling since 1980. Nearly 21 million Americans are believed to have diabetes, according to the Centers for Disease Control, and 41 million more are prediabetic.

"We are particularly excited about Facet's capabilities," said Tim Dugan, Managing Partner with Water Street Capital Partners. "Their engineering expertise and innovation in product development offer a strong platform for continued growth in the exciting and fast-growing blood glucose monitoring business. It also positions the company to grow in related markets that could benefit from Facet's ability to design, develop, and manufacture specialty sharp components and related devices requiring extreme precision and accuracy."

Facet Technologies is an engineering and manufacturing organization providing design, development, and manufacturing services to the medical device industry. The company is a leading designer and manufacturer of hand-held interface devices utilized by patients and end-users.

Eurand Appoints Chief Commercial Officer

Eurand, a specialty pharmaceutical company, recently announced that Mr. John Fraher has been appointed Chief Commercial Officer. In this new position, Mr. Fraher will lead Eurand's commercial and public relations activities and will report to Mr. Gearoid Faherty, CEO of Eurand.

"As Eurand's business expands in the US, Europe, and Japan, we need to provide a more coordinated approach to our global commercial efforts. This appointment will ensure that our licensing, business development, and sales teams in different parts of the world work as one to build our business and provide excellent support to our many customers and businesss partners" said Mr. Faherty. "John's experience, which includes the successful expansion of our presence in the US, will be invaluable as we continue to create new product development partnerships and advance our internal product pipeline."

GlaxoSmithKline & ChemoCentryx Enter Into $1.5 Billion Drug Discovery & Development Alliance in Inflammatory Disorders

GlaxoSmithKline (GSK) and ChemoCentryx, Inc. recently announced a worldwide multitarget strategic alliance to discover, develop, and market novel medicines targeting four chemokine and chemoattractant receptors for the treatment of a variety of inflammatory disorders, including Traficet-EN in late-stage development for the treatment of inflammatory bowel disease (IBD). This collaboration provides GSK access to selected targets from one of the broadest pipelines of chemokine-based therapeutics in the biopharmaceutical industry, leveraging ChemoCentryx's expertise and pioneering insight into the chemokine system. The alliance with GSK will be conducted through its Center of Excellence for External Drug Discovery (CEEDD).

ChemoCentryx will receive an upfront payment of $63.5 million composed of cash and an equity investment in the form of a Series D financing. In addition, ChemoCentryx will receive research funding and will be eligible to earn milestone payments up to, potentially, $1.5 billion, across six product options on the four targets, assuming successful development and commercialization. ChemoCentryx will also receive double-digit royalties on all collaboration product sales and will be able to increase royalties in certain instances by co-funding development through Phase III clinical trials. Furthermore, under certain circumstances, upon an initial public offering by ChemoCentryx, GSK will invest in ChemoCentryx's common stock.

Under the terms of the agreement, ChemoCentryx will be responsible for the discovery and development of small molecule drug candidates targeting four specific chemokine and chemoattractant receptor targets through clinical proof-of-concept, at which point GSK will have exclusive options to license each product for further development and commercialization on a worldwide basis. The agreement encompasses Traficet-EN, a specific CCR9 antagonist currently in a multinational clinical trial (PROTECT-1) of greater than 400 patients with IBD, as well as three ongoing pre-agreed preclinical research programs involving named but undisclosed chemokine and chemoattractant receptor targets. ChemoCentryx will retain the option to co-develop and to co-promote Traficet-EN in IBD to certain physician specialists in the US.

"We are extremely pleased to be working closely with GSK as a premier global pharmaceutical company. Their outstanding commitment to pharmaceutical innovation and broad expertise and experience in the development and commercialization of new medicines in inflammatory conditions make them an ideal collaborator," said Thomas J. Schall, PhD, President and CEO of ChemoCentryx. "This important alliance with GSK will provide us with access to significant capital in the near and long-term to support the ongoing development of each of these programs, as well as the ability to continue to discover and bring forward multiple new compounds targeting the chemokine system."

Maxine Gowen, PhD, Senior Vice President and head of GSK's CEEDD stated, "The ChemoCentryx alliance is a landmark relationship for the CEEDD. This collaboration clearly demonstrates GSK's commitment to gain access to leading-edge, best-anywhere science, and we are excited by the opportunity to work with ChemoCentryx, the leading chemokine company, and their world-class team. Accessing their expertise and four advanced chemokine programs, including Traficet-EN in the clinic for IBD, will allow us to bring novel medicines to patients with high unmet need."

ChemoCentryx has established a broad pipeline of clinical and preclinical stage chemokine-based therapeutics, each targeting distinct chemokine and chemoattractant receptors and offering the potential to treat various diseases. ChemoCentryx is currently conducting the PROTECT-1 Trial for Traficet-EN in patients with moderate-to-severe Crohn's disease, one of the most common forms of IBD. Traficet-EN is intended to control the inappropriate inflammatory response underlying IBD by targeting the CCR9 chemokine receptor. Other programs target receptors that are implicated in a number of inflammatory conditions, including rheumatoid arthritis, multiple sclerosis, systemic lupus erythematosus, acute macular degeneration, and asthma.

ChemoCentryx, Inc. is a clinical-stage biopharmaceutical company focused on discovering, developing, and commercializing orally administered therapeutics that target the chemokine and chemoattractant receptor systems in order to treat autoimmune diseases, inflammatory disorders, and cancer. The chemokine system is a complex network of chemokine molecules, or ligands, and receptors that regulates inflammation. Based on their proprietary drug discovery and drug development platform, ChemoCentryx has generated, internally, several clinical and preclinical stage programs, each targeting distinct chemokine and chemoattractant receptors with different small molecule compounds. The company's compounds are designed to be highly potent with minimal side effects and orally available for improved patient compliance, as well as ease and efficiency of manufacture.

BUSINESS DEVELOPMENT

Strategic Business Development: Positioning for a Liquidity Event

By: Tim Howard, MBA, and Debra Bingham

A question often asked by founders and CEOs of middle market companies is WHEN should they start positioning for a liquidity event? As with most important questions in business, there is no single right answer, and having the right answer does not guarantee success; it is still heavily influenced by the quality of the execution of the answer. In this article, we will provide our thoughts on the WHEN question, we will discuss a framework for planning for a liquidity event, as well as identifying specific actions that you can take to position and optimize the ultimate liquidity event for the company.

Let's start with the simple question of WHY do you want to plan for a liquidity event? If you build a great business, won't people be knocking at your door? Let's be clear, the absolute most important thing that management can do to optimize a liquidity event is build a great company. The purpose of this article is to focus on what else can you do and when should you do it.

In years past, when we spoke of a liquidity event, we were talking primarily about an Initial Public Offering and secondarily about merging or being acquired by another company. Due to the increasingly high market capitalization hurdle and the costs of Sarbanes-Oxley compliance, the IPO market is not an option for most drug delivery or many specialty pharmaceutical companies, leaving a merger or acquisition as the most likely liquidity event. How does one plan for an acquisition a few years down the line? We categorize the necessary activities in three distinct phases described further on.

ASSESSMENT & PLANNING

The Assessment and Planning phase, taking 2 to 4 months, provides the framework that will guide the strategy of the firm as you progress toward a successful liquidity event. During the initial phase, it will be important to:

- quantify owner objectives (financial, timeframe, other);
- identify categories of potential acquirers and establish a strategic fit for each category;
- understand valuation metrics of categories and review recent transactions for validation; and
- delineate strategic gaps of potential acquirers.

Within the context created by understanding the market and the owner's objectives, the next step is to objectively assess whether the current strategy and 3-year plan align with what the market will reward. This process will require the development of a financial model that looks forward 3 to 5 years, integrating market valuation metrics and attainable projections. The business should be managed in a way that maximizes key operating statistics. Similarly, attention should be paid to the balance sheet, ensuring proper capitalization; the last thing you want is to be negotiating a deal with diminishing cash reserves. Invariably, there will be gaps that need to be filled. In filling these gaps, the savvy company can create significant downstream value.

VALUE CREATION

The value creation stage, which can take as little as 6 months but can be prolonged for 2 or more years if required, is all about exploiting your understanding of the market, your areas of need, and when you want to be entertaining liquidity offers. Here is where strategic business development comes to the forefront. Expanding your business and capturing new licenses for your drug delivery technology is critical to demonstrate market validation.

You need to prioritize strategic partnerships with the highest value potential acquirers to fill the gaps you have in your operating plan. This will serve the following purposes, all of which will help to optimize the liquidity:

- eliminate the perception of weaknesses/gaps;
- develop a history of success with strategic partners; and
- establish back channel communication routes

The list of strategic partners that is targeted by business development should align with the list of most likely

acquirers. The deals that are struck should be non-exclusive when possible and have a modest duration. Think of these deals as pilots for the long-term merger relationship that you might consider. Work hard to get visibility for your company throughout various levels of the strategic partner's organization, limiting your executive interaction to peer discussions if possible.

TRANSACTION EXECUTION

Assessment and Planning were done; you created value through your business development efforts, and now you are a few months away from closing a great transaction, right? Wrong! The M&A process will most likely take 6 to 12 months. The process will entail the following:

- preparation of the "Book;"
- assembly of the target list (augment the list of current strategic partners with other potential acquirers);
- qualification of potential acquirers;
- support of preliminary due diligence information requests;
- development of short list of potential acquirers that have a bona fide interest;
- receipt of one or more term sheets;
- selection and negotiation of letter of intent;
- executing the due diligence process;
- negotiatiation of definitive agreement(s);
- closing the transaction; and
- monitoring escrow and/or earn-out period.

Due to the length of the transaction process, it is imperative to ensure that management continues to pay attention to all of the financial and operational metrics identified in the first phase of the process. There is nothing more disheartening than missing quarterly results while in the due diligence process and facing the prospect of a downward price adjustment or being forced to raise a bridge round of capital to make payroll.

WHEN should founders and CEOs start planning for a liquidity event? Start as early as possible but at least 18 to 24 months. Complement planning with focused business development efforts that have the end goal in mind. Lastly, engage in a managed M&A process that results in a competitive bidding situation. You and your shareholders will reap the benefits. ◆

BIOGRAPHIES

Mr. Tim Howard leads the Life Science practice with Stonecroft Capital and has extensive transaction and management experience in the Healthcare and Life Science sectors. Stonecroft Capital is an investment bank dedicated to providing the highest quality strategic advice to growth companies with high potential. Prior to joining Stonecroft, Mr. Howard was Founder and CEO of Galt Associates, Inc., a bioinformatics firm providing solutions to leading biopharmaceutical and medical device companies worldwide. Mr. Howard has twice been selected as an Ernst & Young Entrepreneur of the Year Finalist in the life sciences sector, and led his company to positions in the Deloitte & Touche National Fast 500, and Virginia Fast 50. He has led venture financing, partnering, and acquisition activities and negotiated strategic transactions with 8% of the top 20 global pharmaceutical companies. Mr. Howard currently serves as a Board Member and Advisor to numerous life science companies. His education includes a BS in Physics and Mathematics from Ursinus College, and an MBA from The Wharton School of the University of Pennsylvania.

Ms. Debra Bingham is a Founding Partner of Valeo Partners. She brings clients over a decade of specialized expertise in the pharmaceutical and biotech industries. At Valeo, her primary focus is in helping clients in the areas of business strategy, business development, growth opportunity assessment, and strategic partnering. Ms. Bingham leads Valeo's strategic partnering offering in affiliation with Stonecroft Capital, a DC-based investment bank, which provides full-service transactional capabilities from licensing to M&A. She spent the majority of the past 10 years working in the pharmaceutical industry assisting companies with strategic business assessment and business development. Ms. Bingham has authored many drug delivery business articles and technology reviews and is a featured speaker at industry trade conferences.

Temptation in the Lab: Voluntary Use of Investigational Drugs Without an IND Exemption

By: Natasha Leskovsek, Attorney

Perhaps it is something peculiar to companies investigating novel delivery systems for previously approved drugs. Perhaps the scientific zeal of certain parties close to new technology skews their calculation of potential benefit and risk. Whatever the reason behind the occurrences, when voluntary use of investigational drugs happens without an Investigational New Drug (IND) exemption in place, there are risks not only to the volunteer, but to the academic and/or commercial enterprise interested in formal investigation of the new drug or delivery system. Consider the following examples:

- A company tested a novel formulation of a common antimicrobial on its employees without obtaining their informed consent;
- A research lab employee voluntarily self-administered an investigational formulation of an approved lipid-lowering compound and tested his own blood levels as a very personal proof-of-principle test;
- Laboratory notebooks were found with recorded observations following voluntary intramuscular injection of an experimental drug formulation to test tolerability; and
- Topical and aerosol delivery companies report unauthorized experimentation with their delivery mechanisms prior to establishment of an IND.

Each of these examples is based on facts, and there are surely other cases like them. If there is no immediate harm to the volunteer, what is the problem?

THE REQUIREMENT FOR AN IND

The protection of human subjects and the systematic review of investigational drugs are regulated by sister agencies within the Department of Health and Human Services, the Office for Human Research Protections (OHRP), and the Food and Drug Administration (FDA). Key cornerstones of the regulatory framework are the requirement for subject informed consent and the review of the potential risks to research subjects by an Institutional Review Board and the FDA.

Although the risks of utilizing a previously approved drug in an unapproved new formulation may be thought minimally as the low risk of using a pharmacy-compounded prescription drug, there are at least two issues of importance that separate the approval-directed activities of the former from the self-limited problem-solving of the latter. First, even if the use is anecdotal and voluntary, the consent may not be fully "informed" as there may be unanticipated risks with the new delivery system that the volunteer is not aware of but that the employer and others may be aware of. Those "others" may include competitors whose human experience data is on file with the FDA. Second, whether consent is truly voluntary can be an issue in hindsight if, as typically, no formal consent is documented and the mere appearance of an employer/employee relationship suggests that there may be economic coercion. Finally, it is obvious that such unauthorized experimentation does not yield data that can be later submitted to the FDA as evidence to support the initiation of an IND.

THE CONSEQUENCES

Questionable or bad facts or allegations lead to internal investigations. When company executives or research institution management become aware of occasions of unauthorized use of investigational materials, time and resources must be diverted to determine the scope of the problem, the facts, and to determine potential next steps. Allegations of laboratory misconduct are often made by would-be whistleblowers, further increasing the need for timely and appropriate resolution.

The FDA and OHRP each have enforcement authority over their respective regulations. The FDA's Office of Compliance routinely issues Warning Letters after inspecting clinical investigational sites and finding research to be outside the scope of an IND or deficiencies in informed consent (21 C.F.R. Parts 50 and 312). OHRP's Division of Compliance Oversight also routinely issues determination letters if studies are conducted or supported by a federal department or agency, including federal grant support (45 C.F.R. Part 46). While the real risk of official Agency enforcement in the wake of anecdotal voluntary experimentation described here is questionable, it is important to consider the potential for such enforcement under the extant circumstances.

THE IMPORTANCE OF POLICIES, EDUCATION & CONTROL

The avoidance of even the appearance of laboratory misconduct requires clear policies that are easily understood and followed. Education on the hazards of unauthorized experimentation need to start from the top down because it is often the scientific mavericks of an institution or company that wear blinders regarding the potential risks of such experimentation, both to themselves and to the enterprise. Finally, control over investigational materials is paramount under the circumstances described. While it may be permissible to obtain approved prescription drugs for off-label use, the boundaries of exemption from patent infringement for research in anticipation of regulatory approval are clearly stretched by anecdotal research. For the sake of human subject protection and the integrity of the research enterprise, all such research needs to be in a controlled manner. ◆

BIOGRAPHY

Natasha Leskovsek offers Heller Ehrman White & McAuliffe's LLP Washington, DC, office significant knowledge in both FDA law and clinical healthcare. Her areas of expertise include the regulation of prescription and OTC drugs, medical devices, biologics, and dietary supplements. Ms. Leskovsek is also a registered nurse and served for 6 years as a Clinical Research Nurse in Pediatric Oncology at the National Institutes of Health and as a Regulatory Affairs Professional for a contract research organization. She earned her law degree from Georgetown University and Master of Business Administration and Master of Public Management degrees from the University of Maryland at College Park. The author may be reached at (202) 912-2719 or natasha.leskovsek@hellerehrman.com.

GASTRORETENTIVE DOSAGE FORMS

Clinical Protocol Design for Gastroretentive Dosage Forms

By: Matthew D. Burke, PhD, and Professor Clive G. Wilson

PURPOSE

To highlight key factors of a clinical protocol design that can impact evaluation of gastroretentive dosage forms. Also, to provide a preferred clinical protocol design to allow potential standardization of clinical evaluation and direct comparisons of inventions.

INTRODUCTION

The stomach is a large and more muscular adaptation of the gut, fashioned to form a reservoir that stores food and processes it into chyme. It has the unusual properties of secreting hydrochloric acid and enzymes. To the Scot, the sheep's stomach forms the basis for a national dish (the haggis), and the skin, a favorite musical instrument (the bagpipes). The impression of other nationalities as to the merits of these inventions vary, but to the pharmaceutical scientist, the movement of things in and out of the stomach is a source of many drug delivery patents. The development of a dosage form that can be retained in the stomach is a challenging goal, although the phenomenon has been of interest for longer than most people realize. The first recorded public demonstration of retarded gastric emptying was performed by the Holy Roman Emperor Frederic II (circa 1200 AD), who examined the impact of exercise on gastric emptying after a large meal.1 He ordered two men to eat a large meal and sent one to rest and the other to exercise violently, then killed and disemboweled the men. It was found that the resting man's stomach was empty while the exercised man's stomach was full. Fortunately, in modern times, less lethal clinical endpoints are used for such investigations, although the question still remains: can we accurately predict and control gastric emptying of ingested entities?

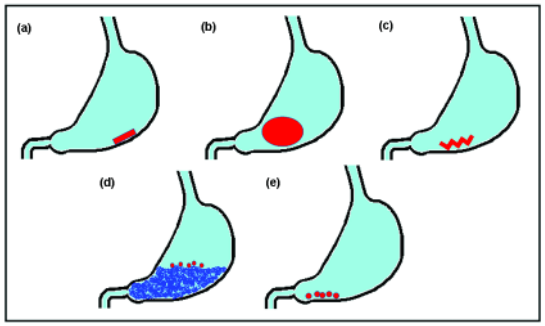
This paper attempts to highlight key clinical aspects for consideration when designing protocols to investigate the performance of gastroretentive dosage forms in man. It is hoped that these observations will assist in the move toward standardized clinical evaluations for direct comparisons of novel inventions.

The common strategies utilized to prolong gastric residence time for dosage forms were recently reviewed by Bardonnet and include (a) bioadhesion, (b) large size, (c) unfolding, (d) floatation, and (e) high density (Figure 1) as well as co-dosing with agents that alter gastric motility.2 Each strategy has advantages and weaknesses. For example, gastroretention based on a large size is believed by some to have the least drawbacks, although the minimum target size and mechanical strength needed to maintain a gastroretentive formulation has not been determined. It has been reported in the endoscopic literature that a 5-cm length by 2-cm diameter rigid object will not pass through the stomach.3,4 Such anecdotal information is useful but not scientifically valid; additionally, the shape of the stomach changes during contraction to form a distal cylindrical space, the pyloric cylinder. Studies by the South African radiologist A.D. Keet have established that the shape and dimensions of the cylinder vary significantly between individuals; whether this will complicate application of gastroretentive technologies is not known.5 Whilst clear identification of the key requirements to achieve a successful gastroretentive formulation in the clinic environment is not established, it is possible to perform clinical studies that examine the advantages a gastroretentive formulation might confer.

THE SIPPING TEST: WILL GASTRORETENTION BE AN ADVANTAGE?

The rationale to pursue a gastroretentive formulation are commonly based on the properties of the drug or a target pharmacokinetic (PK)/pharmacodynamic (PD) profile. For example, a drug may exhibit "difficult" properties, including a short PK and PD half-life, or a localized transporter absorption mechanism, pH-

FIGURE 1



Gastroretentive Dosage Form Mechanisms: (a) Bioadhesion, (b) Large Size, (c) Unfolding, (d) Floatation, (e) High Density

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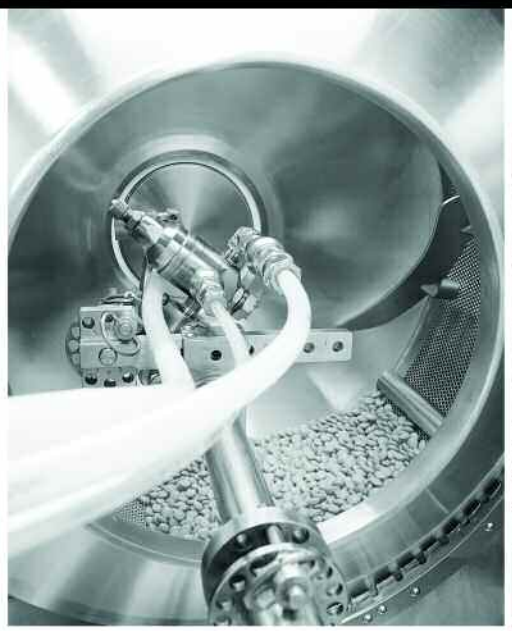

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GASTRORETENTIVE DOSAGE FORMS

TABLE 1

Meal at Time of Dosing	Gastric Emptying Time (hrs)
Fasted	1.0 ± 0.4
Light Breakfast (154 kcal)	2.0 ± 0.9
Heavy Breakfast (795 kcal)	8.8 ± 5.9

Impact of Food on Gastric Emptying of Dosage Forms

dependent solubility, poor transport across the lower small intestine or colon, receptors/targets of interest located only in upper GI tract, and an intestinal absorption window due to slow dissolution in the colon as limited amount of unbound water is available. However, outside of testing the invention, it is also possible to examine the advantages that a gastroretentive formulation might confer. An excellent literature example of this type of clinical study was performed using Acyclovir by Lewis (Figure 2).[6] Lewis and colleagues compared an IR formulation to a sipped solution of the same dose over a 4-hour period. The sipped solution doubled the AUC compared to the tablet. A related clinical study design was utilized internally for a GSK compound, where a single IR tablet dose was compared to 8 sequential doses of 1/8 the total IR dose over a 4-hour period. In this case, the AUC increased by 27%, indicating a benefit in pursuing a gastroretentive formulation (Figure 3).[7] In both cases, careful clinical study design allowed the simulation of advantages that a gastroretentive dosage form might provide before a final design is selected. Translation of these observations into the design of a protocol requires some consideration ahead of the clinical trial to evaluate whether a dosage form is truly gastroretentive.

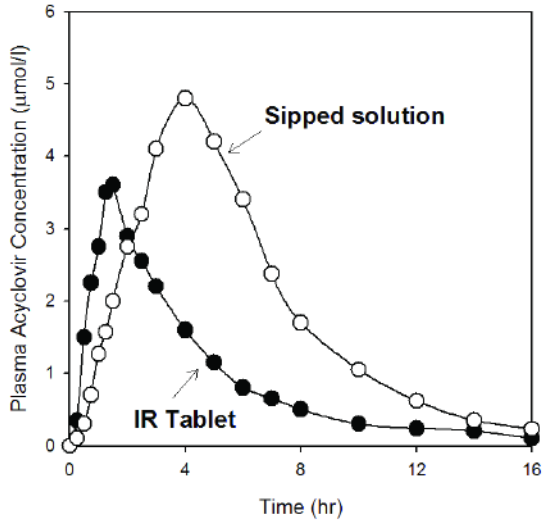
STOMACH MECHANISMS TRYING TO EMPTY THE DOSE FORM: FASTING & FEEDING

The main electrophysiological event controlling gastric emptying of detritus accumulating in the stomach is termed the Migrating Motor Complex (MMC). This can be recorded externally with electrodes on the abdomen. The MMC is characterized by three phases: Phase I, near motor quiescence (45 to 60 min); Phase II, a period of intermittent, apparently random, stationary contractions that are weaker than the Phase III contractions (~30 min); and Phase III, a period of rhythmic contractions with a maximal frequency of two to three contractions per minute in the antrum that cyclically clears the stomach and is often referred to as the "housekeeper wave" (5 to 15 min). During the MMC, the pyloric sphincter or "gatekeeper" of the stomach has been suggested to be almost or periodically closed. For Phase I and II, small particles and liquids pass through, then in coordination with the strong Phase III contractions, the sphincter opens to allow larger entities to be cleared.

In addition to understanding the mechanical digestive forces of the MMC, it is important to consider the role of the duodenum and stomach in regulating the flow of nutrients into the intestines for absorption. It has been reported that food is passed out of the stomach at a rate of (~3 kcal/min).[8] It is clear that food may not empty from the stomach in a linear fashion, and the patterns can be sigmoid, linear, or exponential dependent on the physical state of the meal. In spite of these reservations, this "rule of thumb" is useful to approximate food effects on the performance of the gastroretentive dosage form because Phase III of the MMC will not be initiated until the nutrients have emptied. Therefore, if a person continues to snack during the course of a clinical study and the mechanism by which the gastroretentive dosage form leaves the stomach is a Phase III contraction, evacuation of an intact large dosage form may not occur. A clear example of the effects of food was presented in a paper by Wilson et al (Table 1).[9] A large, radiolabeled sustained-release tablet was administered in the morning in three different dosing scenarios. In all three scenarios, the volunteers were given a morning snack (78 kcal) at 2.5 hours post dose, followed by lunch (995 kcal) at 5.0 hours post dose, and finally an afternoon snack (34 kcal) at 7.5 hours post dose.

When dosed after fasting, the blood sugar is low, and initiation of an MMC is uncertain, thus in mid Phase III, a housekeeper wave might occur immediately flushing the tablet from the stomach. Alternatively, the MMC may be at Phase I, and some time will pass before the Phase III sequence, thus an increased likelihood of tablet retention in the stomach. This poses an interesting problem for expanding systems, which must unfold or

FIGURE 2



Simulation of a Gastricretentive Formulation. Reproduced With Data From Lewis et al.[6]

Lipid Based Drug Delivery Technologies

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TABLE 2

Sequence	Event
1	Evening Meal (~1000 kcal) at 14 hrs predose
2	Overnight fast followed by blood glucose test on arrival at clinic
3	Dose in the morning following a light breakfast (~280 kcal)
4	Water allowed ab libitum but record the quantities ingested
5	Lunch (~1000 kcal) at 5 hrs post dose
6	Afternoon Snack (150 kcal) at 7.5 hrs post dose
7	Evening Meal (~1000 kcal) at 10 hrs post dose

Suggested Clinical Protocol Design for Gastricretentive Dosage Forms

swell at an appropriate rate in gastric conditions to avoid premature evacuation without risk of esophageal obstruction.

In the case of the light breakfast, our rule of thumb (~3 kcal/min) predicts that the food will empty within the hour, and then the stomach would enter Phase III contractions and propel the dosage form out of the stomach. The pattern of MMC is extremely variable within and between subjects, and we have noted that inclusion of a light breakfast in a protocol rather than fasting reduces variability in emptying of intact tablets. When the tablet is dosed with a heavy breakfast, our rule of thumb predicts that the food will empty in approx 4.4 hours; however, the morning snack will add to remnants of breakfast extending this time, in some cases even through lunch. The periodic MMC once initiated will recur every 3 to 4 hours, but the ingestion of food will abolish an existing MMC and restore a digestive pattern of motility. This prolongs the gastric emptying significantly and clearly indicates that an artificially good gastroretentive result can be produced by continual ingestion of food. A similar good outcome can be obtained for floating systems if the volunteer periodically eats and drinks. A note of caution, retention of floating devices is heavily influenced by posture as lying on the right side empties floating objects ahead of a meal. In practice, any marked changes in posture during the trial can have large effects on the emptying of large matrix systems that can find themselves marooned in the proximal stomach.

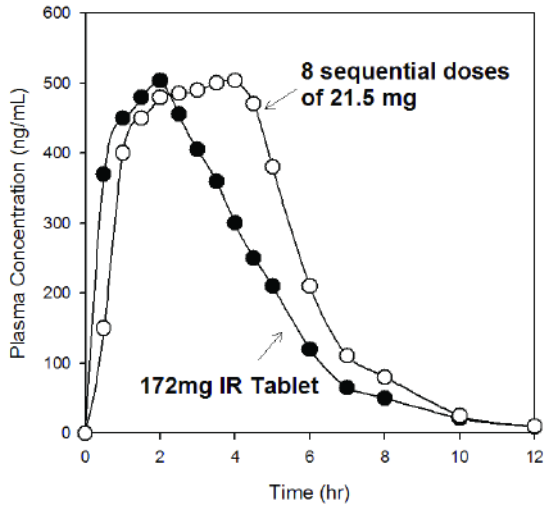
By taking into account the effect of meal size and frequency on gastric emptying and assuming that the Phase III contractions of the stomach are the most challenging phenomena that a gastroretentive dosage form will undergo in the stomach, a suggested clinical protocol design is presented (Table 2).

The rationale for this suggested clinical protocol design is to initially ensure an excessive food intake has not occurred prior to arrival at the clinical site. It is expected that two housekeeper waves (most likely at 10 AM and 1 PM) should occur during the time between breakfast and lunch. The afternoon period rarely proves challenging as the gastric activity subsides in the normal circadian rhythm. A successful gastroretentive dosage form should be able to survive at least two housekeeper waves, surviving into the post lunch period (5+ hours). A normal meal at lunch would probably permit more than an 8-hour retention. Finally, it is important to note that the volunteers should be ambulatory during the study period to simulate a normal day's activity.

MONITORING THE LOCATION OF THE GRDF

Another key aspect of the clinical protocol design is the selection of a technique to monitor the location of the GRF in the gastrointestinal tract. Ideally, a non-invasive approach that does not alter the physical properties of the GRF is preferred, and the frequency of imaging should be at least every 30 minutes for the first 6 to 8 hours followed by every hour until bedtime, resuming in the morning if required. Gamma scintigraphy is often the gold standard for transit studies and has been used extensively for tracking the location of dosage forms *in vivo*. Although the preferred approach, other techniques such as magnetic resonance imaging and fluoroscopy, have been useful. An important aspect of scintigraphy is the ability to use a longer-lived, higher energy

FIGURE 3



Simulation of a Gastricretentive Formulation. Data Courtesy of Dr. Vinod Tuliani.

radionuclide, such as indium-111 to radiolabel the GRF and utilize a second, such as technetium-99m, to radiolabel the food. This allows the outline of and the position of the stomach to be established. It is usual in scintigraphy protocols to image both frontally and laterally to provide geometric mean measurements of radiopharmaceutical release or erosion, although the proper location of the GRF can be captured in single plane images relative to external chest and abdominal markers.

In order to image a GRF using gamma scintigraphy, the radionuclide needs to be retained within the device for an extended period of time. This can pose a serious challenge with large changes in the gastric environment. A novel approach has recently been submitted for publication where the radiopharmaceutical is entrapped in an insoluble polymer melt that is later milled and incorporated as a powder or suspension during the normal manufacturing procedure of a GRF.[10] Whichever technique is utilized, it is important to verify that premature leakage of the radiolabel does not occur as this would confound the interpretation of gastric-emptying data.

As an alternative to visualizing the GRF through direct imaging, one may pursue a pharmacokinetic approach; however, this information is not as definitive. Riboflavin is a common example of a model drug utilized for this purpose; however, caution should be used in interpretation of the PK data to ensure that an improvement in the PK is solely due to gastroretention and not another formulation factor, such as a solubility-increasing excipient or creation of amorphous material. Interpretation of the shape of the irregular PK curve may be confusing as periodic "humps" appear in the plasma concentration-time profile. As the stomach becomes empty, it changes shape, and the greater curvature sags in the abdomen creating a "sump." Periodically, with changes of posture, gastric acid secretion, and intake of liquid, the gastric sump volume containing the released drug is moved to the intestines. However, in this interpretation, it is important to exclude enterohepatic recirculation or entero-enteric recirculation, which could also result in the humps in the PK profile.

SUMMARY

In conclusion, clinical protocol design is a critical factor when evaluating gastroretentive formulations in man, which can significantly impact the clinical outcome, and this short review has attempted to present known pitfalls. There remain many other important topics to consider, outside of the scope of this article, which include the selection of appropriate in vitro dissolution techniques (none has been agreed yet), proper use of preclinical models (dogs differ from man in the regularity of the MMC), and other biopharmaceutical issues. The benefits of a robust but safe gastroretentive formulation are clear to the pharmaceutical industry and continue to fuel interest in academia and industry.

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BIOGRAPHIES

Dr. Matthew D. Burke currently serves as an Investigator at GlaxoSmithKline in the Product Development division of Pharmaceutical Development in the Research Triangle Park site. While working at GSK, his responsibilities have included ensuring the delivery of drug products for clinical evaluation and market introduction, assurance of constructive collaborations with external partners, development and implementation of drug delivery systems, drug delivery platforms, and specialized analytical technologies. Within GSK, Dr. Burke served as co-chair of an international drug delivery network that assessed oral, inhalation, transdermal, and buccal delivery systems. Dr. Burke has approximately 20 articles, patents, and symposia presentations. He is an adjunct assistant professor in the Biomolecular and Chemical Engineering department at North Carolina State University and on the Executive Advisory Board of the Drug Delivery Technology magazine. He is an active member of the American Association of Pharmaceutical Scientists and American Chemical Society. Dr. Burke earned his BS in Biochemistry and Chemical Engineering from Virginia Tech and his MS and PhD in Chemical Engineering from North Carolina State University.

Professor Clive G. Wilson holds the JP Todd Chair of Pharmaceutics at Strathclyde University in Scotland, although currently he is on a sabbatical research period. His work has focused on the use of imaging techniques in formulation research, and he has received the Amersham and Pfizer awards in recognition of his contribution to this field. His main areas of research are the relationship between gastrointestinal physiology and drug absorption and the problems of ocular drug delivery. He has supervised more than 40 PhD students and has authored over 400 publications that include original articles, reviews, and six books. The publications reflect his interest in imaging, physics, drug absorption and metabolism, and pharmacokinetics. He is a member of the editorial board of the *European Journal of Pharmaceutics and Biopharmaceutics* and Editor of the Taylor & Francis series in pharmaceutical technology.

The World of Hand-Held Injection Systems

By: Cindy H. Dubin

INTRODUCTION

Biopharmaceutical research and development is sure to significantly increase the number of injectable drugs coming to market throughout the next few years. While advanced drug delivery techniques continue to hold promise for unique methods of administration, the traditional injection is still the dominant paradigm. However, the staggering costs and intransigent safety problems associated with sharps, along with consumer demand and the move to alternate-site care, are pushing for alternatives to traditional needles (needle-free or needle-based) and syringes faster than advanced delivery technologies can come online.

The alternative in the short-term appears to be the growing industry of needle-free injection and safety-engineered syringes. These devices, ranging from simple sheathed safety needles to complex gas jet injection systems, are competing in a vigorous marketplace, some sectors of which are growing at an annual rate in excess of 20% and should reach $2.49 billion by 2009, according to a new study from market research firm Kalorama Information, a division of MarketResearch.com.

As the discovery and development of new drugs create the promise of relief and improved levels of care for a variety of chronic conditions, developers are increasingly aware of the need to pair these promising new therapies, more than half of which cannot be taken orally, with delivery methods that are patient friendly and that encourage compliance. These combination products, in which the delivery device is an integral part of the approved drug therapy, must take into account the needs of a broad range of end-users, including elderly patients and those with compromised dexterity, a rapidly growing demographic segment of the population in developed countries. For many drug developers, the answer to this challenge will increasingly be needle-free injection.

Intraject® is a prefilled, single-use disposable system being developed as a needle-free treatment for migraines

REVIEWING THE NEEDLE-FREE INJECTION MARKET

In June 2003, Greystone Associates predicted that the NFI market would grow from $10.2 million in 2002 to $425 million by 2007, with 54% of these sales being insulin-based. One of the most commonly used technologies in needle-free delivery is jet injection in which a compression system (mechanical or gas) is used to accelerate drug particles to a relatively high velocity and pressure, allowing them to penetrate the skin and be deposited subcutaneously, intramuscularly, or into the epidermis. User-friendly designs and the availability of an increasing number of drugs in prefilled disposable cartridges and syringes are propelling the growth of injector pens at the expense of other drug delivery methods, such as traditional syringes. Advances in synthetic materials and concurrent development partnerships between pen designers and drug developers are important factors in the growth of this segment. Already a leading drug delivery method in Europe (more than half of all diabetics in Europe administer insulin via pen injectors), pen growth will expand as new therapies, particularly for HRT, become available for pen devices.

Accoring to industry experts, the NFI market is being driven by two forces. First, there is concern in the healthcare community about needlestick incidents. Well over 1 billion vaccine doses are delivered worldwide by hypodermic injection every year. This number is expected to grow considerably throughout the next 10 years due to an increase in immunization coverage of target populations and the addition of new vaccines to World Health Organization's (WHO) immunization program. The incidence of needlestick injuries, particularly in developing countries, is also anticipated to increase significantly if a safer injection alternative is not implemented.

The second driving force is contamination, according to Larry Petersen, Executive Vice President of Injex, who says exposure to needles is great and that a needle out of the arm is a weapon. A needleless

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system offers no residual contamination. People don't dispose of needles properly, and a needle-free system avoids the chance of contamination in this instance, he adds.

Antares Pharma Focuses on Diabetes and HGH

Antares Pharma's Medi-Jector VISION® is used worldwide for delivering insulin. Sales in 2005 of Medi-Jector and disposable products reached approximately $1.4 million. The company manufactures other devices for pharmaceutical partners that are branded under various names, including ZomaJet® 2 Vision, SciToJet™, and Twin-Jector® EZ II marketed in Europe and Asia for daily injections of human growth hormone (HGH). Medi-Jector VISION uses pressure to create a micro-thin stream of insulin that penetrates the skin and is deposited into the subcutaneous tissue in a fraction of a second.

The company is developing a new needle-free injector, Valeo™, which features a smaller power pack and a self-contained medicinal cartridge. While Pete Sadowski, Vice President Device Group at Antares, could not comment on the therapeutic focus of Valeo (the company does have needle-free injection devices used for delivering insulin and HGH), he did say that a prototype of the device has undergone both preclinical and clinical testing. Valeo is designed to compete with cartridge-based, pen-like devices that use replaceable needles.

"The company believes that with the increasing incidence of diabetes coupled with an increasing awareness of this disease, the benefits of tightly controlling diabetes will become more widely known, and the number of insulin injections self-administered by people with diabetes will increase," says Mr. Sadowski. "The need to increase the number of insulin injections given per day may also motivate patients with diabetes to seek alternatives to traditional needles and syringes."

Medi-Jector VISION® Needle-Free Injection System

Aradigm Halts Investment in Intraject

Despite significant clinical success during the past few years, Aradigm announced this past May that it has ceased further significant investment in its Intraject technology, a prefilled disposable needle-free delivery system that allows a patient to comfortably self-administer drugs to the subcutaneous or fatty region under the skin. From there, the drug enters the systemic circulation with an identical pharmacokinetic profile as seen with conventional needle-based subcutaneous injection. Intraject technology was developed throughout the past 9 years and has been evaluated in clinical trials involving more than 700 subjects given more than 4,000 injections. Intraject is composed of two main parts: the glass capsule with a prefilled volume of 0.5 ml, and a compact nitrogen gas power source (the actuator). To use Intraject, the patient snaps off the plastic tip (which acts as a sterile seal), flips the lever into the active position, and presses the device against an area of the skin to activate delivery. The delivery process is completed in less than 60 milliseconds.

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When asked about the future of Intraject by *Drug Delivery Technology* magazine, the company referred to a printed statement by Dr. Bryan Lawlis, CEO of Aradigm, that read, "In early 2005, Aradigm aggressively began partnering discussions on Intraject following completion of commercial design and *in vivo* and *in vitro* trials. Partnering Intraject has taken longer than we first anticipated when we acquired the technology. However, we stated over 6 months ago that interest in Intraject is high, that we expect to have term sheets in the first quarter of this year, and that a transaction could be expected by the end of the second quarter. During that period, we also stated that we did not expect to invest further in this platform, instead preferring to invest in our higher value pulmonary products. However, the deals available to us — while they have some value — do not fully cover the costs of development before commercialization. Therefore, a simple partnering would allow us to participate in the value of Intraject while not having to invest further in it, which could take the form of spinning it off into an independently financed company or selling it."

Caretek Medical Ltd's Needle-Free, Transdermal Drug Delivery Technology, ImplaJect®

Bioject to Develop a Disposable Cartridge Jet Injection System for Global Immunizations

Bioject Medical Technologies, Inc., has signed a long-term collaboration agreement with PATH, an international, nonprofit organization, for the development of a single-use, needle-free, disposable cartridge jet injection system for global immunizations. According to Mike Redmond, Senior VP of Business Development, the project has achieved an early-stage prototype called VitaVax. Trials are scheduled to begin within the next year.

Extensive focus groups were conducted in collaboration with PATH to determine the need of developing-country immunization programs. Many clinics in developing countries gave their input as to their specific needs and best ways to use such needle-free technology, leading Bioject to design this new injection system. This new product will be able to meet the immunization challenges posed domestically and in the developing world as it utilizes injection cartridges that are easy to fill, needle-free, single-use, autodisabled, fully disposable, and low cost. The system consists of a small, hand-held injector with disposable cartridges that administer safe and reproducible injections, which requires no external power supply.

Jim O'Shea, Chairman, President, and CEO of Bioject, says he hopes this development program will not only include PATH, but other global health organizations that also have expressed interest in providing assistance and funding to deliver needle-free immunizations in the developing world. "We expect that in the near future, the product being developed under this agreement will also be used to deliver lower doses of vaccine intradermally, enhancing the availability of vaccines such as influenza." A clinical trial has been scheduled for early 2006 to test this dose-sparing

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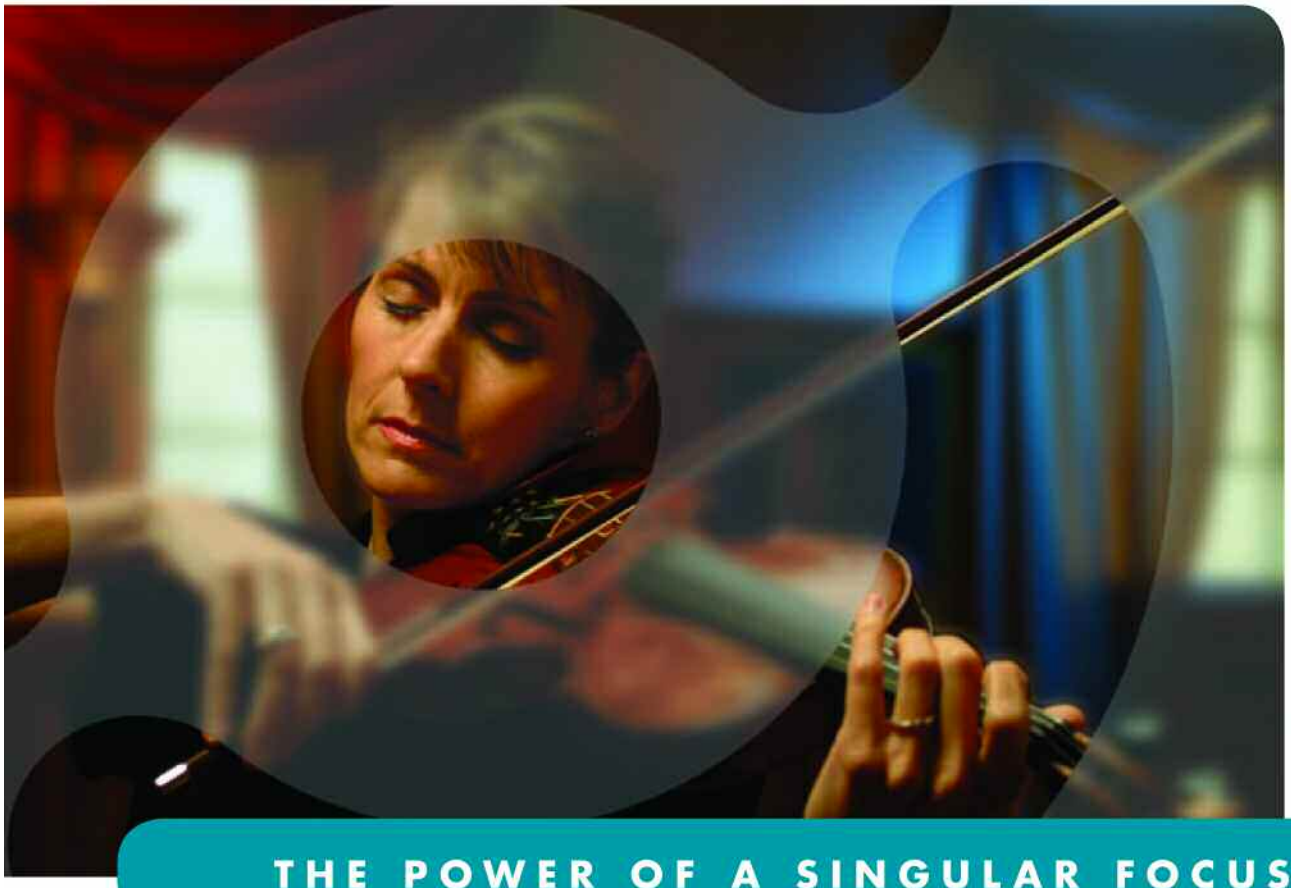

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Currently available are the Biojector® 2000, a CO_2-powered system that delivers subcutaneous injections, and is being used for intradermal injections in clinical trials; and the Vitajet® Needle-Free Injection System, designed for subcutaneous self-injection of insulin in the home. Vitajet has a reusable injector and a disposable nozzle. The Vitajet uses a spring-based power source.

Going forward, Mr. Redmond says that Bioject will concentrate on prefilled needle-free systems because of their convenience and safety issues. "Prefilled needle-based systems have worked well and if we can prefill needle-free systems, that will propel the NFI market," he says.

Bioject entered into several clinical studies with Roche and Trimeris to provide clinical data for the use of its B2000 device with their drug Fuzeonn. In November 2005, Roche and Trimeris received an "approvable letter" from the FDA in response to their request for inclusion of information about the B2000 needle-free injection device in the Fuzeon (enfuvirtide) labeling. In the "approvable" letter, the FDA requested additional information from an ongoing "With a Needle-Free Device" (WAND) study, which is a randomized, open-label, two-way, cross-over study that assesses the tolerability of the B2000 device for administration of Fuzeon. This study is expected to be completed in the second quarter of 2006, and Bioject expects that Roche will receive FDA clearance in the first quarter of 2007.

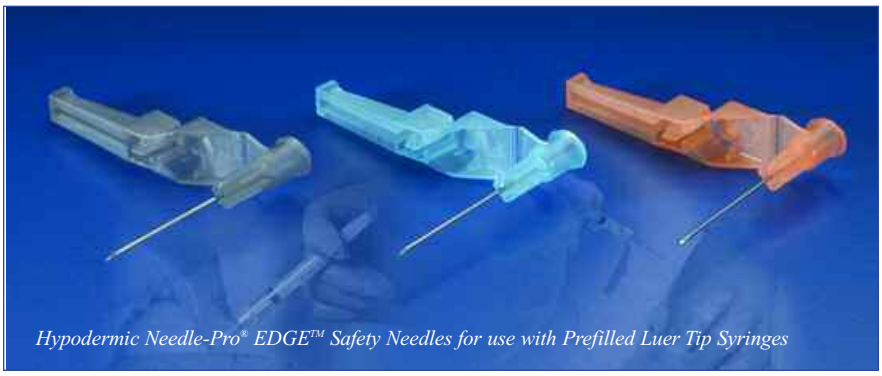
In November and December 2005, Bioject entered into three project agreements with Merial, whereby Bioject will perform feasibility analyses for a next-generation Vetjet device for the companion animal market, as well as for devices for the production animal and poultry markets. Merial currently markets Bioject's Vetjet device for use with its feline leukemia vaccine.

Caretek to Inject Migraine Meds & More

Caretek Medical Ltd's needle-free, transdermal drug delivery technology, ImplaJect®, pushes a pharmaceutical formulation in a solid, semi-solid, or liquid form directly through the skin of a human or animal using the needleless, spring-powered device. In its simplest form, the needle-free drug delivery technology comprises an inert, dissolvable pioneer tip that is pushed against, pierces, and penetrates the skin. The pioneer tip has one pointed end located close to the outer end of the drug cassette in the delivery device. The other end of the pioneer tip is flat and is in close proximity or joined to the drug in the drug cassette.

The device is prepared by inserting the drug cassette into the end of the reusable body. To actuate the system, the end of the drug cassette is placed against the skin, and the reusable body of the device is pushed toward the skin. The process of pushing the system against the skin primes the internal driving spring, and when fully primed, allows it to actuate automatically. This has an inherent safety feature built in such that if the driving spring is not fully charged and the injection is aborted, then the drug cassette can be safely removed from the device.

Caretek recently announced the selection of Sumatriptan Succinate as its lead drug compound at the Needle-Free and Auto Injector Conference in London. Sumatriptan is currently prescribed in tablet form to treat migraine, which affects around 12% of the UK population. Caretek



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- Eliminates dosing errors due to poor injection technique
- Eliminates off-label "dose splitting"

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plans to develop a solid form of the drug that will be suitable for patients to inject using ImplaJect.

The market for the sole existing injectable migraine drug, a form of Sumatriptan that is known as Imigran in the UK and Imitrex in the US, and delivered via needle and syringe, was approximately $220 million in 2005. In recent focus group discussions with Imigran users, the migraine sufferers showed enthusiasm for Caretek's needle-free device, which is easier to assemble, use, and dispose of than their current medication, and could provide fast, reliable relief for their symptoms.

Dr. Charles Potter, Caretek's Founder and CEO and inventor of ImplaJect, said, "We have demonstrated that we can develop generic products, such as Sumatriptan, with much shorter development times than for new drugs. We hope to start clinical trials later this year with the objective of launching a new product that is suitable for use with ImplaJect onto the market in 2008."

Dr. Andrew Dowson, Director of the Headache Service at King's College, London, and Chairman of the Migraine in Primary Care Advisor Group (MIPCA), says the injections can provide Sumatriptan's speed of effect in 10 minutes after injection, compared with 30 minutes in tablet form.

Caretek hopes that Sumatriptan will be the first of a range of solid-form drugs developed for use with the ImplaJect device, and is exploring collaborations with pharmaceutical companies. Dr. Potter says there is potential to develop other products. "Many drugs, such as insulin, vaccines, and emergency pain relief, cannot be administered by mouth because they will not be adequately absorbed in the body or will not act quickly enough, so they are delivered in liquid form via needle and syringe. This is an uncomfortable process that carries a risk of infection. ImplaJect could provide a user-friendly and cost-effective alternative method to deliver many protein-based drugs in solid form. We are interested in exploring partnering opportunities to co-develop the technology for both generic and proprietary medicines."

DCI Applying for FDA Clearance

The LectraJet® HS high-speed jet injection system from D'Antonio Consultants International (DCI) was designed for mass immunization campaigns. The system is available with an electrically armed or a lower cost manually armed device. The Centers for Disease Control and Prevention (CDC) and WHO have identified the need for an easy-to-use, reliable, rapidly deployable needle-free injector that provides protection against pre-injection vaccine contamination and eliminates the risk of cross-infection for the billions of vaccinations given annually. The LectraJet HS delivery rate is better than the 600 injections per hour as requested by the CDC, and uses autodisabling, single-shot, low-cost disposable cartridges that eliminate the risk of pre-injection contamination and post-injection cross-infection associated with the older style multi-use nozzle jet injectors and with needle and syringe reuse. A numerical display shows the number of injections delivered over the life of the injector as well as during a particular session.

Cartridges are housed in a sterile magazine and can be prefilled by the drug manufacturer or on-site directly from the vaccine vial. The filling procedure can also be done directly from a reconstitution syringe. The filling process is extremely rapid, removing the incentive to fill in advance.

"LectraJet is unique in that there is no need for the healthcare worker to ever touch the cartridge, thus eliminating the risk of contamination before an injection and the risk of cross-infection from bloodborne pathogens after the injection," explains Mr. Nick F. D'Antonio, Sr., President of DCI.

Once field trials — expected to begin late summer/early fall 2006 in the Baltimore area and in Africa — are

TABLE 1 - Various Hand-Held Injection Systems & Accessories

Company	Technology	Status	Description
Antares Pharma	Valeo™	Has undergone preclinical and clinical testing	Designed to compete with cartridge-based, pen-like devices that use replaceable needles
Aradigm Corp.	Intraject	Late-stage development for Sumatriptan for migraines, investment halted	Prefilled, single-use disposable system that administers drug to the subcutaneous layer without use of needle
BD Medical - Pharmaceutical Systems	BD Liquid-Dry™ Injector, BD™ Pen II & BD Hypak SCF™ Glass Prefillable Syringes	Commercialized	The Injector allows the patient to reconstitute and inject with a single device. The Pen II offers multi-dose capabilities. BD Hypak SCF™ is a convenient, easy-to-use, prefilled drug delivery system offering accurate, premeasured doses contributing to reduced medication errors.
Bioject	Biojector® 2000	FDA approved	CO_2-powered system for intramuscular and subcutaneous injections
Caretek Medical Ltd	ImplaJect® delivering Sumatriptan Succinate	Clinical trials to start late 2006; product launch in 2008	NFI device for delivering Sumatriptan to migraine sufferers
D'Antonio Consultants International Inc.	LectraJet® HS-P	Clinical trials planned for summer & fall of 2006; applied for FDA 510K	High-speed, light-weight, mobile, hand-held, NFI system, capable of over 60 shots/min with single-use, self-destruct cartridges that never have to be touched by the healthcare worker
Injex-Equidyne Systems, Inc.	Injex 30, Injex 50, and Jet Syringe (Rojex)	Injex 30 and 50 are on the market; Rojex is in final phase of development and testing	Injex 30 and 50 are NFI systems to administer various medications that require subcutaneous injection; Rojex is an all-disposable, single-use NFI
King Pharmaceuticals	ComboPen®	FDA and international regulatory agency approved	Single-use, disposable autoinjector that delivers a single intramuscular injection up to 2 mL. This technology is utilized in several of King's autoinjector products, including Vanquix™ and EpiPen®
Smiths Medical ASD, Inc.	Hypdermic Needle-Pro® EDGE™	Currently available	Safety device for use with prefilled glass syringes
Ypsomed (w/Safety Syringe, Inc.)	UltraSafe Passive® Auto-injector	Available 2007	Ypsomed and Safety Syringe, Inc. have collaborated on this development, resulting in a solution that combines Ypsomed's reusable autoinjector that accommodates a prefilled syringe with SSI's UltraSafe delivery system

completed, LectraJet will be classified for FDA clearance. Mr. D'Antonio expects this to happen in about 18 months.

DCI and its pharma partners (the names are anonymous) have also made a proposal to the Department of Health and Human Services to answer the call for an avian flu vaccine along with a proposed variable-dose version of its LectraJet for delivery. This system will feature the DCI cartridge with a short perforator that goes into the skin to the proper depth prior to delivery. "If we are awarded a contract for this program, we will work with two vaccine developers to "stretch" the available vaccine over a greater number of people in the US population and elsewhere around the world, if possible," says Mr. D'Antonio.

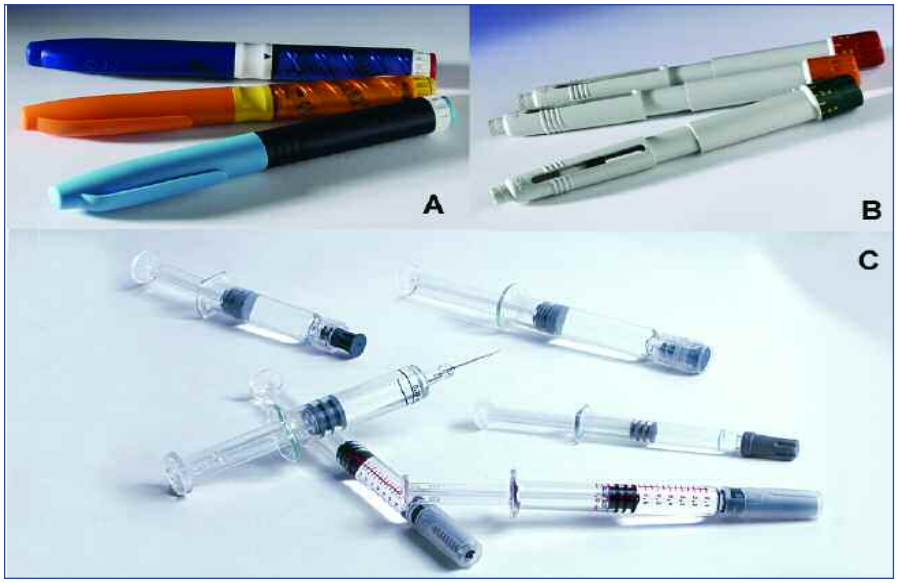
Injex Enters Third-World Market

Injex is a well-established firm in the NFI industry and has recently entered the prefilled NFI market sector with its new single-use inert ampule that is prefillable with a variety of injectable medications. Injex has been in active discussions with both the WHO and the CDC regarding projects that will utilize Injex NFI technology to provide needle-free vaccinations in third-world countries, where the reality of spreading contagious diseases using needle syringes is a constant threat. Mr. Petersen indicates that WHO administers approximately 1.4 billion needle syringe injections annually.

Injex also offers single-use, all-disposable systems that are best suited for short-term or infrequent therapies or in applications where either convenience or ease of use are indicated. Through its ongoing R&D program, Injex has introduced products into the pipeline that will enable the delivery of larger dose volumes per injection, enhance ease of use, and provide convenient prefilled systems for fixed-dose applications. They include:

- Injex 50 — a reusable needle-free injection system that utilizes single-use disposable ampules. The system is capable of delivering from 0.10 to 0.50 mL per injection. Injex 50 is best suited for long-term therapies, such as insulin and HGH, as well as for pediatric vaccinations and other subcutaneous injections given in a clinical setting. Ampules are filled from standard medication vials using the Injex Vial Adapter.

- Jet Syringe — a disposable needle-free injector can be configured with either an adjustable dose "fill-and-shoot" ampule or a proprietary prefilled ampule for fixed-dose applications. Dose volume of delivery is up to 0.5 mL. A general use 510(k) clearance has been granted for administration of subcutaneous injections. The Jet Syringe utilizes a mechanical (non-gas) energy source. This system is



The BD™ Pen II (A) is a full-featured, high-quality pen injector offering reliability, value, and variable and multi-dose capabilities. The BD Liquid-Dry™ Injector (B) allows the patient to reconstitute and inject with a single device. In only seconds, the patient can have the drug reconstituted, primed and ready for injection without the use of additional needles or complicated reconstitution devices. The BD Hypak SCF™ (C) is a convenient, easy-to-use, prefilled drug delivery system that offers accurate, premeasured doses contributing to reduced medication errors.

ideally suited for short-term and infrequent injection therapies, and the prefill version is also ideal for vaccines given via subcutaneous injection.

- Prefilled Ampule — compatible with either reusable or disposable Injex devices. Fixed-dose volume capacity up to 0.5 mL. The ampule has a tiny orifice that is smaller in diameter than one strand of human hair. Medicine is propelled through this orifice at supersonic speed and is desposited into the subcutaneous tissue. When properly used, the injections are essentially painless, says Mr. Petersen.

- Injex 100 — for injections of larger dose volumes, this model will deliver up to 1.0 mL of liquid medication in one delivery, and a minimum dose volume of at least 0.8 mL. Injex 100 is used only for subcutaneous drug delivery.

NEEDLE-BASED SYSTEMS

The reality is that not all drugs can be delivered via needle-free injection, and some industry insiders even argue that NFIs might have bioequivalency issues when compared to a needle injection. Thus, key players like BD Medical – Pharmaceutical Systems, King Pharmaceuticals, and Ypsomed are continuing to make great strides in needle-based systems. Part of their efforts include sharps safety manufacturers. Following the passing of Federal legislation in the US mandating the use of sharps safety devices within the healthcare setting, the awareness by pharmaceutical companies as to the need for safety is increasing. Consider the relationship between Ypsomed and Safety Syringes discussed further.

While there is no requirement that pharmaceutical companies must deliver their injectable products utilizing either prefilled or disposable syringes with needle-safety devices, the decision to include safety devices as a value-added feature is currently being considered by many in their product life-cycle management.

"In addition to the ethical reasons for adding safety, by doing so, it provides pharmaceutical companies with the ability to gain competitive advantage over their competitors who have not yet implemented safety solutions," says Mark Baumgartner, Business Development Manager, International/Pharmaceutical, Smiths Medical ASD, Inc.

Smiths Medical has responded to these needs by further developing its Hypodermic Needle-Pro® EDGE™ product line. With key features, such as no added dead space, which minimizes overfill volumes and medication wastage and color-coded safety sheaths to rapidly identify needle gauge, this new needle-safety device provides the clinician with benefits of safety, convenience, and cost effectiveness, says Mr. Baumgartner.

BD Sees Growth of Self Injection

According to Mr. Michael Ratigan, Worldwide Self-Injection Platform Director, BD Medical – Pharmaceutical Systems, the company is an established player in the hand-held injection market, providing self-injection devices to serve the fertility, hepatitis C, and HGH markets. Currently, the company has cartridge-based pen systems and dual-chamber reconstitution pen systems on the market. Developmental efforts include new technologies and next-generation devices.

Mr. Ratigan says that BD anticipates the self-injection market growing at 15% compounded annually. Growth drivers

include, but are not limited to, disease incidence and prevalence, economics, home healthcare preference, and technology advancements. BD Medical – Pharmaceutical Systems is leveraging its current customer base and intellectual property to introduce next-generation devices and new technologies to ensure future growth.

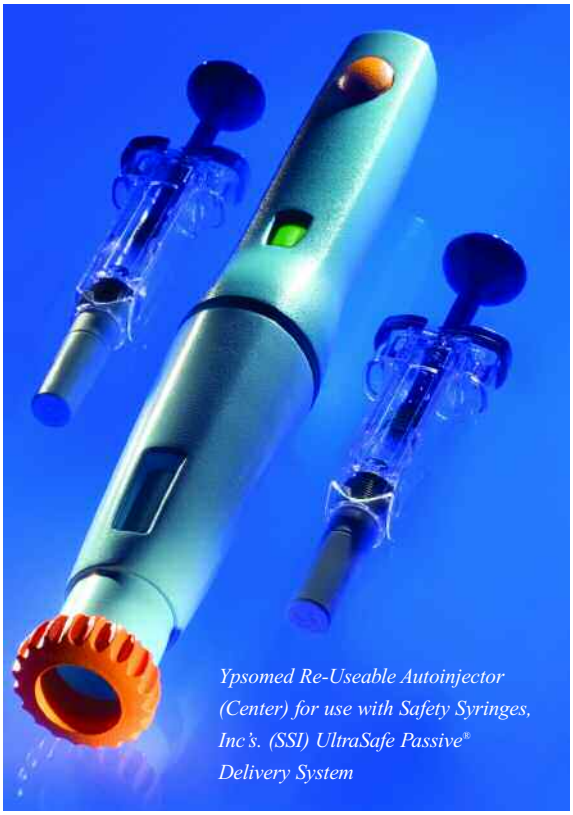
The most exciting developments in hand-held injection technology include market introduction of latest-generation autoinjectors, the majority of which utilize the BD Hypak SCF™ syringe. BD Hypak SCF is a convenient, easy-to-use, prefilled drug delivery system that offers accurate, premeasured doses contributing to reduced medication errors. As the demand for convenient and safe prefilled delivery systems is growing, the quality and efficiency of BD Hypak SCF glass prefillable syringes truly differentiate pharmaceutical products from those in vials or ampoules as well as other drug delivery systems, says Mr. Ratigan.

Additionally, BD Medical – Pharmaceutical Systems recognizes the issues linked to sharps-related injuries. BD offers an extensive array of safety-engineered injection products, such as BD Preventis™, a prefilled syringe, automatic needle shielding system. Mr. Ratigan says that BD's continued investment in safety technology shows its commitment to providing innovative products and solutions for the future.

King's Vanquix® in Phase III Trials

In January, King Pharmaceuticals, Inc., commenced a Phase III clinical trial program evaluating its investigational drug Vanquix as a treatment for acute, repetitive seizures associated with epilepsy. The active ingredient in Vanquix is diazepam, which is administered using King's autoinjector technology.

According to Tom Handel, Vice President-Alliance Management & Commercial Pharmaceuticals at King, there is no commercially available adjunctive injectable therapy, outside of a hospital setting, for the emergency treatment of acute, repetitive epileptic seizures. At present, the only product commercially available for the management of patients with acute, repetitive seizures by a caregiver other than a healthcare professional is a diazepam rectal gel. This product requires a patient to retain the gel in the rectum for absorption to occur and may be difficult to administer during a seizure. Furthermore, the rectal route of administration may be considered objectionable to many patients and caregivers, particularly in a public setting. Vanquix administers a therapeutic dose of diazepam intramuscularly.



Ypsomed Re-Useable Autoinjector (Center) for use with Safety Syringes, Inc's. (SSI) UltraSafe Passive® Delivery System

For almost 50 years, King has distributed more than 185 million autoinjectors to more than 40 countries. The initial regulatory application for Vanquix will be submitted to the FDA, but the company is also targeting the filing of Vanquix outside the US.

Mr. Handel says that King is unique in that it is the only fully integrated autoinjector company that designs, develops, manufactures, assembles, and sells/markets this type of technology.

Currently marketed products utilizing King's autoinjector technology include EpiPen® (epinephrine), the emergency treatment for severe anaphylaxis, AtroPen® (atropine injection) and the Mark I® Nerve Agent Antidote Kit. Mr. Handel says that needle-based autoinjector systems are ideal for the emergency administration of medication. Patients remove the safety release and apply a firm pressure to the outer thigh. The device is automatically activated and the drug is delivered. "This technology will administer the dose through multiple layers of clothing, including the chemical protective enables worn for military and first-responder personnel," says Mr. Handel.

Ypsomed Focuses On Pens & Auto Injectors

Ypsomed AG develops and manufactures custom-made injection-pens and compatible pen needles for a range of pharmaceutical partners. The product line ranges from simple disposable pens to pens with variable dose setting and electronic display. Ypsomed's growth in recent years has been driven by the increased use of disposable self-injection devices.

Aging population demographics and

managed care initiatives are major forces driving the growth of home healthcare, a trend that includes the self-administration of drug therapies for chronic conditions, such as diabetes, arthritis, and hormone replacement therapy, says Mr. Ian Thompson, Manager, Business Development.

The company is working with a number of pharma partners for its new range of autoinjectors based on 2-spring injection technology. The disposable autoinjector is aimed mainly at the RA/autoimmune and emergency drugs markets and incorporates the key features of simple and intuitive use with "interlock/button" activation, 2-stage injection, audible and visual end of injection feedback, and needle safety. Ypsomed is also collaborating with Safety Syringes, Inc., on a reusable autoinjector for use with the UltraSafe® delivery system. The device allows Safety Syringes' pharmaceutical partners to ensure that there is no exposure to potential needlestick injuries. UltraSafe is designed for prefilled glass syringes. As the dose is completed, the safety guard passively locks into place to protect from sharp inuries. The design is currently being finalized following patient-handling studies.

According to Mr. Mark Hassett, Vice President Marketing and Business Development, the reusable autoinjector will be used for cancer therapies performed in the clinic and at home; and for chronic home therapies like multiple sclerosis and rheumatoid arthritis. The relationship with Ypsomed marks Safety Syringes' first partnership with a device company and another will be happening down the road, Mr. Hassett adds.

OUTLOOK

Annual needlestick injuries in the US alone average 600,000 to 1 million, and estimates indicate that as many as 80% of the incidents could be prevented with the use of needle-free devices and safety syringes. A new report, Needle-Free Injection Systems and Safety Syringes: The Market for Alternatives to Needle-Based Delivery, predicts that the exorbitant costs associated with needlesticks — costing institutions more than $3,000 per injury even when no infection occurs — coupled with other factors, such as patient fear of needles and the resulting lack of compliance, are strong enough drivers to grow the market by a compounded annual rate of 11% throughout the next 4 years. Whether the devices are insulin pens for diabetics or mono-dose vaccine injectors, developing newer and safer ways of administering a wide variety of drug therapies is here to stay, even if such devices do come with a higher price tag.

"Certainly the development, testing, regulatory approval, and eventual mass manufacturing of such devices is not cheap, yet the costs need to be continually weighed against the greater benefit to global health," notes Mr. Joseph Constance, the report's author. "With newer injectable drugs coming to market and incidences of diseases requiring injectables, such as diabetes, escalating worldwide, the need for safer devices will continue to grow the market."

Fortunately, cost-effective and reliable devices have begun to appear with the convergence of synthetic materials and computerized design software. New designs currently being developed will create new opportunities for needle-free injection. "Reusable injectors designed to accept prefilled syringes or drug cartridges will improve ease-of-use and increase needle-free injection's share of the growing self-injection market," explains Mr. George Perros, Greystone Managing Director. Disposable prefilled NFI models will penetrate selected practitioner segments, such as wellness vaccines. "Partnerships between needle-free injection suppliers and pharmaceutical companies will foster market acceptance of NFI for a host of new therapies, such as therapeutic vaccines, DNA-based drugs, and protein-derived biologics," adds Mr. Perros. ◆

BIOGRAPHY

Ms. Cindy H. Dubin has been a professional journalist since 1988. She is currently the Editor-In-Chief of Specialty Pharma magazine and is a Contributing Editor to Drug Delivery Technology. 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.

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The Accordion Pill®: Overcoming the Absorption Limit in the GI Tract

By: Michel Afargan, PhD, and Noa Lapidot, PhD

INTRODUCTION

Oral dosing is by far the most convenient route for drug administration when systemic absorption is required. However, for many drugs, the blood levels that can be achieved by the oral route are often limited by 1) rapid drug elimination and 2) significant absorption only occurring in a short section of the GI tract. Therapeutic blood levels are achieved for only a short period of time, as the dosage form releasing the drug transits out of the stomach and along the GI tract. This results in a need for frequent dosing with a danger of poor patient compliance, relatively little of the drug absorbed actually reaching the systemic circulation (ie, low bioavailability), the levels that are achieved are not steady but fluctuate and variable, and toxicity associated with unavoidable high C_{max} levels. All these factors make the safety and efficacy profile of the drug suboptimal and difficult to control and are an outcome of the inherent pharmacokinetic properties of the drug. Standard extended-release formulations do not offer much advantage as once they leave stomach, the released drug is no longer in a region where it can be absorbed. In some cases, these challenges are so significant that a drug cannot be dosed orally, leaving either parenteral routes as the only alternative or switching to another drug altogether. For a drug in development, this can mean the termination of the development program.

The phenomonen of an absorption window is closely related to the chemical and physical properties of the drug molecule, the luminal milieu, and the mechanisms of its transport across the intestinal barrier to the blood circulation. Active substances that are selectively transported by carriers that are prevalent in the upper parts of the GI include amino acid analogues (widely used as CNS drugs), nucleoside analogues (used as anti-viral drugs), peptidomimetic molecules (used in cardiovascular treatment), and beta-lactam antibiotics.

A rational approach to enhance bioavailability and improve the pharmacokinetic/ pharmacodynamic profile is to retain the drug reservoir proximal to its absorption area, ie, in the stomach and to release the drug as a controlled oral infusion for a prolonged period of time. The need for gastroretentive dosage forms (GRDFs) to make the most use of drugs with unforgiving characteristics has led to extensive efforts in both academia and industry in the development of such drug delivery systems.[1,2]

MARKET VALUE OF ORAL GR DRUGS

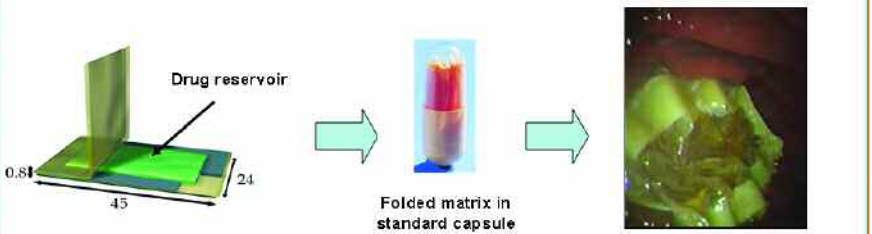
The market value of drugs that would benefit from gastric retention is large, estimated at more than $30 billion. The categories of drugs that may be significantly improved include:

- Amino Acids Analogs (eg, various drugs for CNS disorders)
- Small Peptide Peptidomimetics (eg, cardiovascular drugs)
- Beta-lactams and Cephalosporins (antibiotics)
- Nucleoside Analogs (eg, various antiviral drugs)

Another scenario that could benefit from gastric retention and controlled release in the stomach would be the directed local therapy in the treatment of pathologies located in the stomach, the duodenum, or upper small intestine.

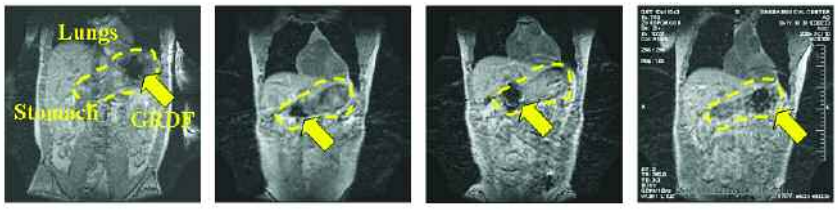
Reformulation in a controlled release-gastric-retention (CR-GR) system offers a unique approach to life-cycle management (LCM) of drugs in which the patent is expiring or generic forms

FIGURE 1



The GRDF laminated structure (left), which is folded in a standard capsule like an accordion (middle), and is unfolded in the stomach (right) as visualized by gastroscopy of a healthy volunteer 15 minutes after swallowing.

FIGURE 2



MRI images of magnetite-labeled GRDF in a human volunteer, given after a light breakfast. At 5 hours post dosing, a lunch of about 800 kcal was given. At 24 hours, the labeled GRDF was not visualized anywhere in the GI tract, implying evacuation of the dosage form within 24 hours.

have already appeared. LCM allows for faster and less risky development programs, with three times higher success rate at Phase I compared to new drug entities, and as such, are widely utilized by pharmaceutical companies to maximize revenues.

At the other extreme, a revolutionary business opportunity for an effective novel and efficient gastric-retention CR system might be to convert the route of administration for certain drugs, ie, from injectable to oral.

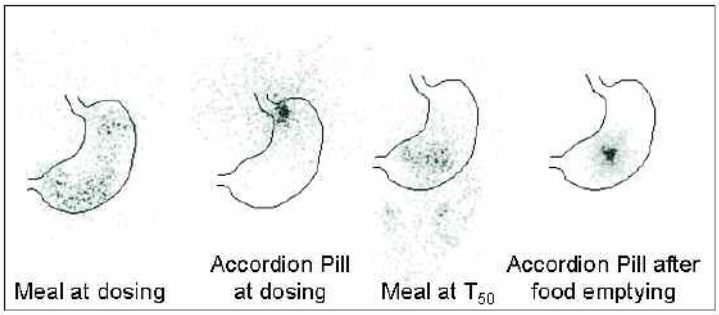
THE FAST & FED STATES OF THE STOMACH

The process of GI transit in humans and its implications on attaining gastric retention and drug delivery are well appreciated.[3] Gastric emptying is controlled by the feeding status: high calorie and high fat food extend the time before emptying of the stomach of solids, and emptying time is typically 3 to 5 hours. In the fasted state, the stomach is evacuated of its remaining content by the "housekeeping" wave that occurs irregularly. Most objects larger than 20 mm will be retained in a fed stomach, while objects smaller than 5 mm are likely to be evacuated even in the presence of a meal. To achieve prolonged gastric retention, a drug must be delivered in a formulation that resists evacuation by propagated waves of contraction in the stomach, and can also withstand the harsh environment of the stomach, which is functionally designed to triturate solid material.

DEVELOPMENT OF THE ACCORDION PILL® GASTRIC-RETENTION SYSTEM

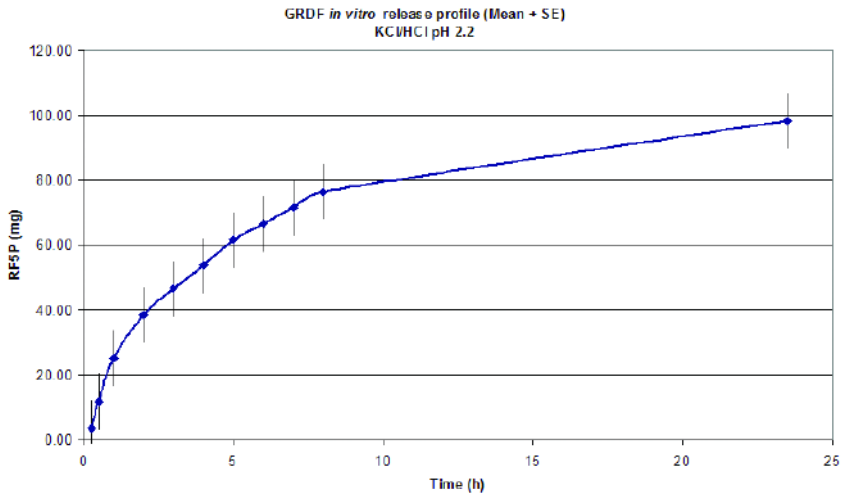
Considering the environment of the stomach, a gastric-retention (GR) system should provide effective retention in the stomach to extend exposure whilst maintaining the convenient and familiar appearance of conventional oral formulations to facilitate patient compliance. In this respect, it is important that patients are not obliged to always take the GR-formulated drug with high calorie meals, but can carry on with their regular diet. The oral form should provide sufficient drug-loading capacity; should degrade and be evacuated once the drug release phase is over; should display no effect on gastric motility (including emptying pattern of subsequently ingested doses); and be free from adverse local effects. In addition, to achieve optimal release profiles for drugs with varying characteristics, fine control of the release rate should also be possible.

FIGURE 3



γ-scintigraphy images of (from left to right): labeled meal immediately after dosing; the GRDF immediately after dosing; 50% evacuation of the meal (0.77 + 0.12 h vs. 0.21 + 0.13 h (SE) for the control tablet); (D) the GRDF retained in the stomach after the meal has fully evacuated (14.3 + 3.7 h vs. 3.7 + 0.4 h for (SE) the control tablet).

FIGURE 4



In vitro release profile of RF5P in KCl/HCl buffer, pH 2.2.

Ideally, control over the drug-release rate and the drug-release profile should be independent of the retention properties of the system.

The accordion-like gastric-retentive dosage form (GRDF) was designed and developed to meet these demands (Figure 1).[4] The GRDF consists of a laminate of polymeric layers, some of which are responsible for the mechanical properties required to achieve retention in the stomach, while others are responsible for holding the drug and controlling its release rate. The laminate is folded and enclosed inside a standard gelatin capsule. Once exposed to the gastric fluid, the capsule dissolves, the GRDF unfolds, and drug release begins.

The GRDF has been studied in a series of clinical trials to assess its retention in the stomach, as well as its safety and efficacy of enhancing the absorbance of a model drug for drugs that are poorly absorbed due to a transporter-dependent, region-specific absorbance pattern. Highlights of recent clinical trials are described further.

STUDY OF RETENTION PROPERTIES

To follow the fate of a dosage form that is designed to be retained in the stomach, the accordion-like dosage form was formulated with ferric oxide (magnetite), an MRI contrasting agent, in the drug reservoir film. Human volunteers were given the magnetite-labeled GRDFs after eating a light breakfast (282 kcal). The retained dosage forms could be visualized with MRI, and typical results are presented in Figure 2. The GRDF was shown to move in the stomach during the retention phase, and did not appear to obstruct the pylorus, thus minimizing the risk of interference with the passage of gastric contents into the duodenum.

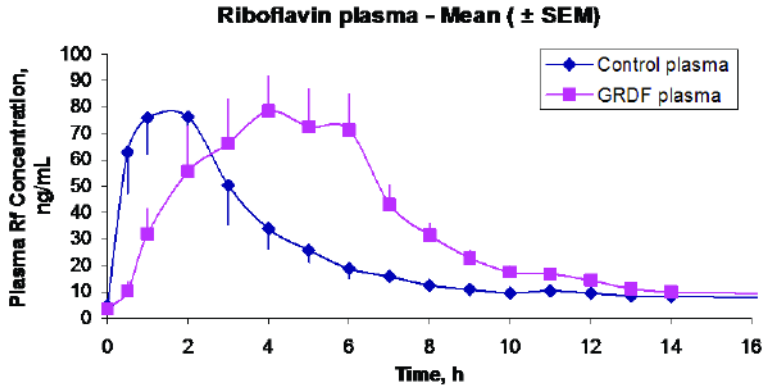
In this clinical trial, all five subjects retained the dosage form for 6 hours, four out of the five retained it for 12 hours. In all five subjects, the GRDF was evacuated from the stomach by 24 hours (MRI images were not taken between 12 and 24 hours). This study was repeated with a group of eight volunteers in which six of eight subjects retained the GRDF for 10.5 hours, all evacuated the GRDF by 24 hours (no images were taken between 10.5 and 24 hours). One person evacuated between 3 and 4.5 hours; the other person evacuated between 4.5 and 6 hours.

FOOD EMPTYING IN THE PRESENCE OF THE GRDF

An important safety concern with any expandable (or swelling) gastric-retentive dosage form is the possible hindrance of emptying of food or of other drugs. To evaluate this, the GRDF was labelled with a ^{111}In – marker and taken with ^{99m}Tc – labeled food. The food and the GRDF could therefore be followed simultaneously by a γ-camera. A large non-disintegrating tablet, also labeled with ^{111}In was used as a comparator arm with the labeled food in this study. The trial was carried out in a random cross-over design in eight healthy volunteers. Figure 3 presents typical images obtained, showing the meal in the ^{99m}Tc channel and the GRDF in the ^{111}In channel.

In this trial, the mean T_{50} and T_{90} for food evacuation from the stomach were 0.77 (± 0.12) hour and 1.43 (± 0.13) hour for the GRDF, while the control times were 0.71 (± 0.13) hour and 1.51 (± 0.21) hour, respectively. We therefore conclude that the GRDF does not affect food emptying. This γ-scintigraphy trial also confirmed the retention times observed by MRI because in four volunteers, the GRDF evacuated from the stomach between 18 and 24 hours (no images were taken between these two times), two evacuated by 5.5 hours, one by 4 hours, and one by 3.75 hours.

FIGURE 5



Mean plasma concentration of RF dosed after a light meal with an IR formulation (blue) or a GRDF (purple).

INCREASED BIOAVAILABILITY

The same GRDF platform was used for a riboflavin formulation (RF), which was selected as a model drug substance. This vitamin is known to be preferentially absorbed in the upper GI by a specific, saturable transporter.[5] The cumulative release rate of riboflavin in KCl/HCl buffer at pH 2.2 was 80% at 10 hours, in the same range of time that the GRDF was shown to be retained in the stomach (Figure 4).

In a double-cross over trial, the RF-GRDF was dosed after a light breakfast to seven volunteers, affording a 65% increase in bioavailability of the API as compared to an immediate-release formulation. The absorption phase was extended from ~4 hours in the control capsule to ~8 hours with the GRDF, C_{max} was similar in both cases (78 ng/ml) while T_{apical} was extended from ~1.5 hours to ~5 hours (corresponding T_{max} values were 1.5 and 3.5 hours, respectively). The mean plasma concentration of RF of the GRDF and the control IR formulation are both presented in Figure 5. This clinical trial confirmed that holding of the drug reservoir in the stomach while releasing the drug continuously over the same period of time can effectively enhance bioavailability, even when the absorption is limited by saturation of a specific transporter.

CONCLUSIONS

Recent clinical studies have demonstrated that Intec's Accordion Pill™ achieves outstanding gastric retention with controlled drug release. This unique approach offers a remarkable opportunity whereby reformulation can significantly enhance the safety, efficacy, and convenience of many orally administered drugs.

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BIOGRAPHIES

Dr. Michael Afargan is VP of Clinical Development for Intec Pharma. He is an expert in biopharmacy, with over 12 years of experience in the biopharmaceutical industry. Formerly the CEO and Founder of HPBM Ltd., an Israeli biopharmaceutical company established in 1999 that provides an R&D network for applied pharmacology, including early ADMET, PK, and PD, lead discovery and selection for preclinical stages. Dr. Afargan was the Founder of the Israeli consortium Pharmalogica, active in the biopharmaceutical development of novel prediction tools-early ADMET. Dr. Afargan has five academic degrees; BSc and MSc (studies) in Life Sciences of Ben-Gurion University, Beer-Sheva, Israel. Pharmacist (BPharm), MSc Pharm, and PhD (Medicinal Chemistry and Pharmaceutical Sciences) of the Hebrew University, Jerusalem, Israel.

Dr. Noa Lapidot is VP of Research & Development for Intec Pharma, serving as the head of the R&D department since 2004. In 1998, Dr. Lapidot co-founded Sol-Gel Technologies, which developed microencapsulation for pharmaceutical and cosmetics, where she served as R&D Manager and the IP Manager until 2003. From 2003 to 2004, she participated as Researcher and Coordinator in a state-of-the-art project at The Hebrew University in the fields of nanoelectronics, scanning microscopy, and surface chemistry (EU FP5 project). Between 1994 and 1997, Dr. Lapidot was a Senior Researcher at Electric Fuel (today Arotech), responsible for materials (polymeric materials, metal coating), zinc electro-regeneration, and analytics. From 1993 to 1994, she served as an Analytical Chemist at the R&D Department of Teva Pharmaceutical Industries. She earned her PhD (1993) and BSc (1986) in Chemistry from The Hebrew University of Jerusalem.

PRECLINICAL EVALUATION

The Characterization of Preclinical Research Dogs Using a Combination of pH Monitoring & Gamma Scintigraphy

By: Erin Peters and Ann Vickers

INTRODUCTION

Preclinical evaluation of compounds and drug delivery technologies is a critical step in the drug development process. Research animals provide the means for this, but care must be taken to understand the impact of factors such as gastrointestinal pH and transit times on formulation performance. The Bravo™ pH System (Medtronic, Inc.) is a catheter-free, pH-monitoring system that allows for up to 48 hours of constant pH data collection. The data is transmitted from a small capsule (ingested orally) to an external receiver, which is then downloaded to pH analysis software on a computer workstation. The ability to use the pH system concomitantly with an imaging modality such as gamma scintigraphy would validate pH readings with location in the gastrointestinal (GI) tract. To the best of our knowledge, prior to this study, the Bravo pH System had not previously been used with gamma scintigraphy. The Biopharmaceutics Imaging Lab at GlaxoSmithKline was able to successfully radiolabel and document pH readings from Bravo pH capsules in vivo, using both beagle and mongrel dogs. Gamma scintigraphy provided the ability to track the radiolabeled Bravo capsules, correlating the pH readings with location in the GI tract.

TECHNOLOGIES

Scintigraphic images were acquired using a Siemens e.Cam dual-head fixed 180º Single Photon Emission Computed Tomography (SPECT) camera. The camera head was fitted with a medium-energy parallel-hole collimator placed ventrally beneath each dog. Frames were acquired every 60 seconds. Gastrointestinal pH monitoring was performed using the Bravo pH System. The following details are for the Bravo pH System:

Bravo pH Capsule (Figure 1): A radiotelemetric pH-monitoring device. The capsule transmits pH readings from the surrounding environment to the data recorder device every 6 seconds, on a 433-mHz frequency. The capsules were purchased from Medtronic, Inc. and have approximate dimensions of 2.5 cm x 0.6 cm x 0.4 cm.

Data Recorder Device: Receives radio frequency transmissions from the capsule. The recorder can collect data from either 24-hour or 48-hour pH-monitoring studies.

Polygram Net Analysis Software: Data from the recorder device was downloaded to a computer workstation containing this software. The software allowed for comprehensive pH data analysis.

FIGURE 1

Bravo™ pH Capsule

After calibration, the Bravo pH capsules were radiolabeled with Indium^{111} Chloride (Photon Imaging). A small piece of heat-shrink tubing was used to affix Indium^{111}-labeled tissue paper to the outer shell of each capsule.

STUDY DESIGN

In Vivo Dosing

The Bravo™ pH capsules were radiolabeled with approximately 45 µCi

In^{111} chloride and dosed orally in both beagle and mongrel dogs. The capsules were dosed with 20 cc of water given via a syringe. The following variables were evaluated:

- Gastrointestinal pH under fed condition
- Gastrointestinal pH under fasted condition
- Gastric pH using 40 cc of 0.05N HCl predose gavage (beagle dogs only)
- Gastric pH using 6 µg/kg pentagastrin IM predose treatment (beagle dogs only)

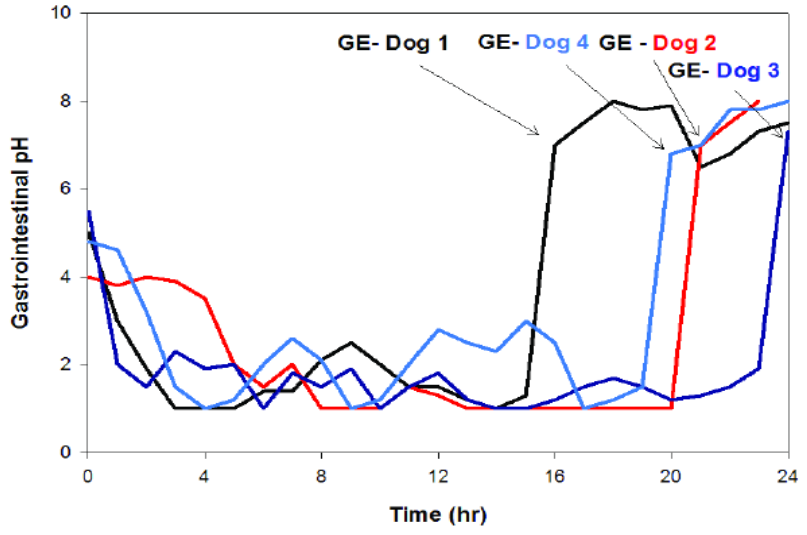
Gamma Scintigraphy

Prior to the start of the study, all of the dogs were trained to lie quietly on the gamma camera bed (with the detector positioned ventrally) during the imaging sessions. No anesthesia was necessary. Each dog was imaged immediately following dosing and then throughout the study day at 30 to 60 minute intervals, until approximately 8 hours post dose. By the morning of the following day, the capsules were visualized (using the gamma camera) to be in the colon.

RESULTS

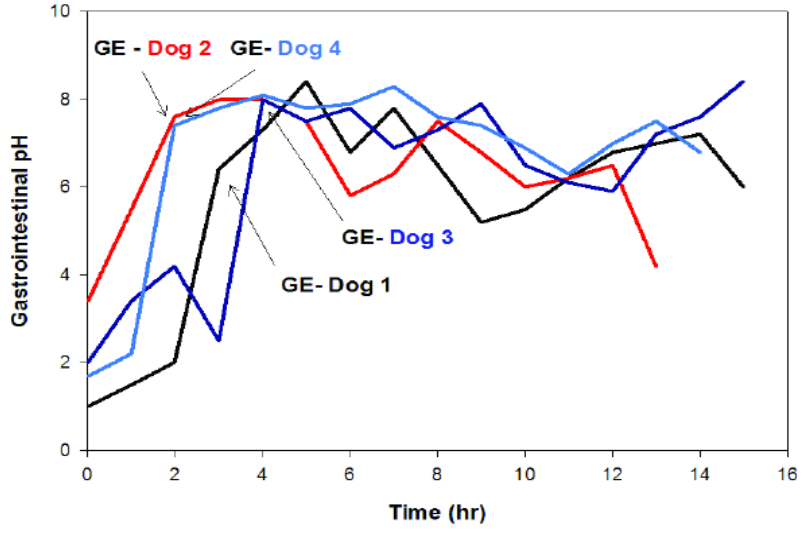
By visually observing the readout on the data recorder devices, pH readings were obtained and recorded throughout the study day. The gamma camera provided confirmation of gastric residence times and GI transit times for the capsules throughout each study day. For the fed portions of the study, the mongrels' gastric pH ranged from 1.0 to 5.5, with gastric emptying (GE) ranging from 16 to 23 hours (Figure 2). The beagles' fed gastric pH was similar to the mongrel dogs' and ranged from 0.8 to 4.3, with GE occurring earlier than the mongrels,' ranging from 7.5 to 8 hours (Figure 4). Under fasted conditions, the data for beagles and mongrels proved very similar: gastric pH ranged from 1.0 to 7.2 (mongrels, Figure 3) and 1.8 to 7.8 (beagles, Figure 5); gastric residence time (GRT) for the pH capsules ranged from 1 to 3 hours (mongrels) and 0.25 to 1.92 hours (beagles). The mongrel dogs appear to be over-predictors for gastric retention when compared to the beagles, which is significant to note if considering mongrels for gastric retention formulation work. We

FIGURE 2



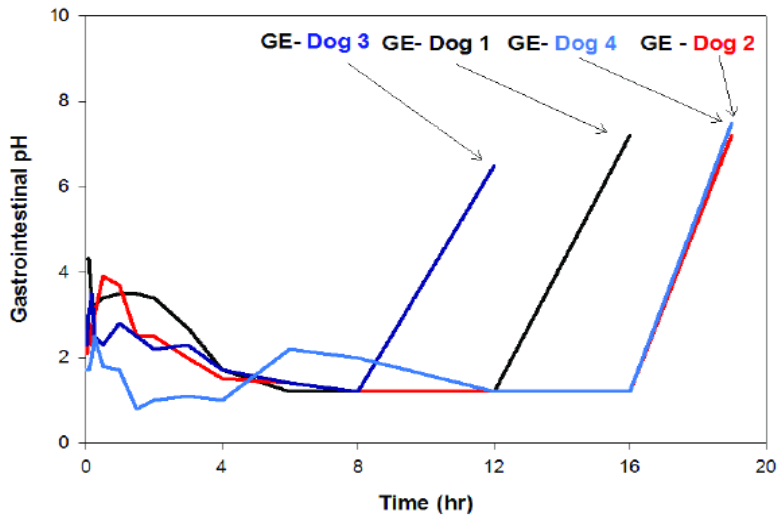
Gastrointestinal pH of Fed Mongrel Dogs (Gastric Emptying Was Determined by Gamma Scintigraphy and is Noted by the Arrow)

FIGURE 3



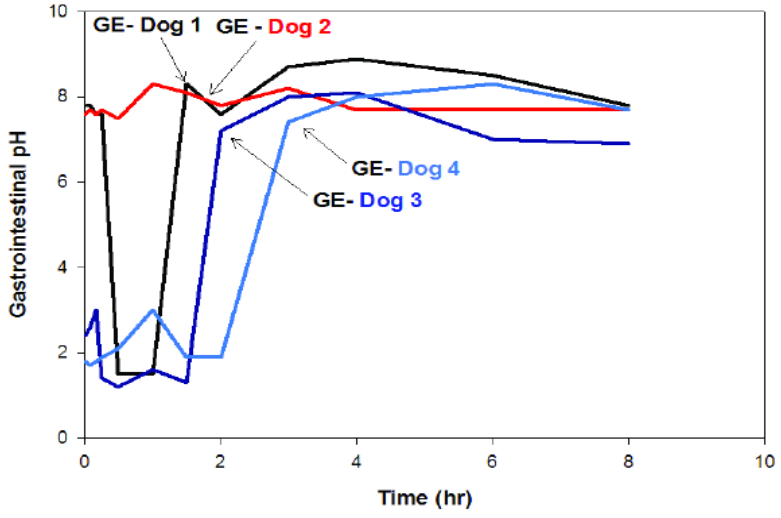
Gastrointestinal pH of Fasted Mongrel Dogs (Gastric Emptying Was Determined by Gamma Scintigraphy and is Noted by the Arrow)

FIGURE 4



Gastrointestinal pH of Fed Beagle Dogs (Gastric Emptying Was Determined by Gamma Scintigraphy and is Noted by the Arrow)

FIGURE 5



Gastrointestinal pH of Fasted Beagle Dogs (Gastric Emptying Was Determined by Gamma Scintigraphy and is Noted by the Arrow)

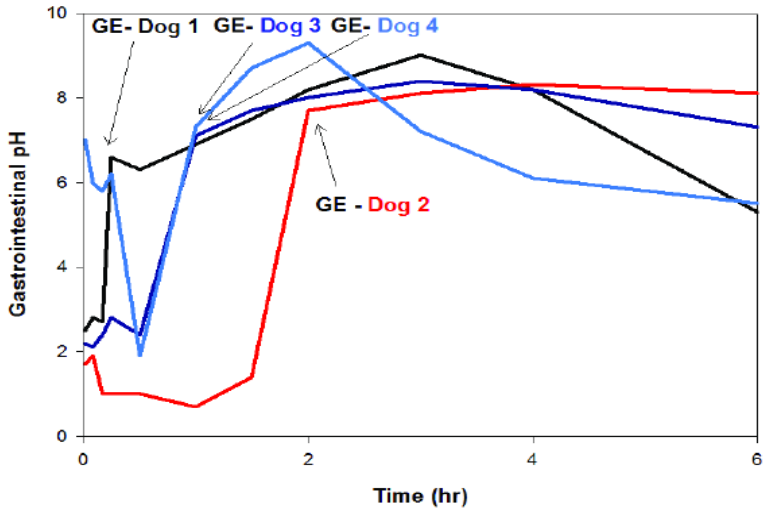
found that radiolabeling the pH capsules was extremely useful in verifying gastric residence times, particularly when the stomach pH and small intestinal pH were similar, making it impossible to distinguish gastric emptying based solely on pH readings.

Another factor pertinent to drug and drug delivery technology development is the fact that gastric pH in the fasted dog (both mongrel and beagle) is somewhat variable and can be quite high. Therefore, in vivo studies were performed with beagle dogs to investigate pretreatment techniques to artificially reduce the pH. These techniques allow scientists to better mimic human gastric pH conditions in the fasted state. We were surprised by the variability in gastric pH after gavage with HCl (Figure 6). In two of the dogs dosed, the stomach pH remained at acidic levels (0.5 to 2.8) until gastric emptying. One of the dogs, however, was able to neutralize the acid after 10 minutes, raising the gastric pH to alkaline levels prior to gastric emptying. The fourth dog saw a drop in gastric pH, but not until 15 minutes following dosing, immediately prior to gastric emptying of the pH capsule. Pentagastrin produced much more consistent results (Figure 7). When administered 20 to 30 minutes prior to dosing, all of the dogs experienced a gradual decline in gastric pH prior to gastric emptying of the pH capsule.

SUMMARY

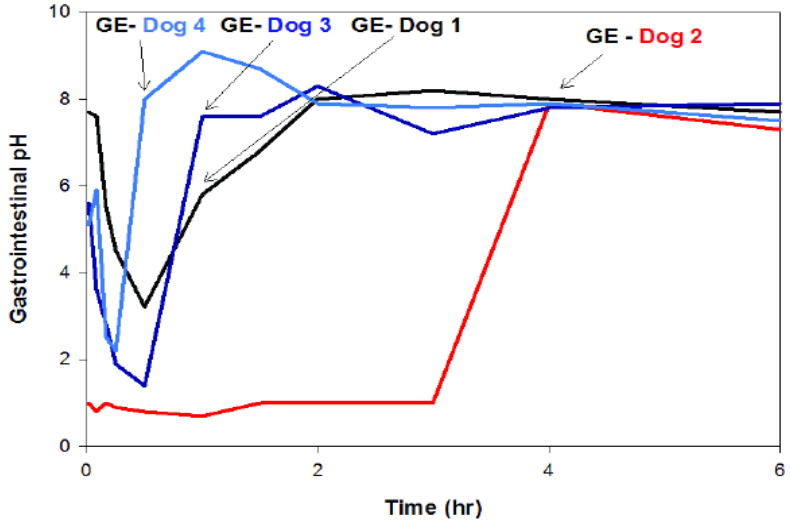
The preclinical gamma scintigraphy laboratory at GlaxoSmithKline has successfully radiolabeled and dosed pH-recording capsules in beagle and mongrel dogs. As a result of these experiments, gamma scintigraphy and radiotelemetric pH monitoring were found to be compatible technologies. Because we know that interpreting pharmacokinetic study results can oftentimes be confusing, obtaining accurate pH readings from the gastrointestinal (GI) tracts of our research dogs had been a long-term goal. We were able to obtain comprehensive pH data, as well as solid dosage form transit data from the GI tracts of our dogs, incorporating several variables. Understanding and characterizing the in vivo functionality of research animals is critical for accurate drug and drug delivery technology

FIGURE 6



Gastric pH of Fasted Beagle Dogs using 40 cc of 0.05N HCl Predose Gavage (Gastric Emptying Was Determined by Gamma Scintigraphy and is Noted by the Arrow)

FIGURE 7



Gastric pH of Fasted Beagle Dogs Using 6 Ìg/kg Pentagastrin IM Predose Treatment (Gastric Emptying Was Determined by Gamma Scintigraphy and is Noted by the Arrow)

development. Many dosage forms and drug delivery systems are pH dependent, and characterizing the GI tracts of the dogs has provided accurate in vivo correlation data to supplement experiments. Knowing as much as possible about various gastrointestinal parameters in preclinical animal models can assist researchers in optimizing their drug delivery technologies, saving time, money, and resources in the long run.

BIOGRAPHIES

Ms. Erin E. Peters has been a Scientist with GlaxoSmithKline since 2002. Currently, she is the Principle Investigator for the Scintigraphic Imaging Laboratory at GSK's RTP-North Carolina site. Ms. Peters designs, executes, and reports on in vitro and in vivo research studies as part of the Biopharmaceutics division in Preclinical Development. Her areas of expertise include animal model development, nuclear imaging, PK studies, capsule endoscopy, pH monitoring, and gastrointestinal transit studies. Prior to her work with GSK, Ms. Peters was employed by North Carolina State University's College of Veterinary Medicine. While at the NCSU-CVM, she conducted feline retroviral research and HIV vaccine development based on the characterization of cytokine and protein expression in lymphoid and hematopoietic tissues. Ms. Peters earned her BS in Zoology from North Carolina State University.

Ms. Ann W. Vickers is a Scientist with the Biopharmaceutics Division of GlaxoSmithKline in Research Triangle Park, NC. Ms. Vickers was one of the co-founders of the Scintigraphic Imaging Laboratory at the GSK-RTP site and has extensive experience in the field of nuclear imaging. She holds an undergraduate degree in Psychology from North Carolina State University and a Masters in Exercise Physiology from East Carolina University in Greenville, NC.

TRANSDERMAL MARKET

The Future of Transdermal Drug Delivery Relies on Active Patch Technology

By: Jason McKinnie, Frost & Sullivan Analyst

INTRODUCTION

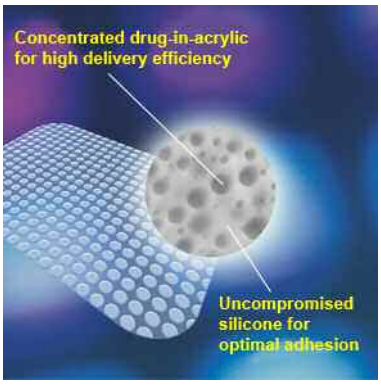
For 25 years, passive patch technology has dominated the transdermal drug delivery industry. Evolving from the simplistic drug reservoir to a complicated matrix design, passive patches have navigated many of the difficulties of transdermal drug delivery and overcome obstacles by utilizing better adhesives, increased drug storage, and better regulated release, all with decreasing overall patch size. Despite these accomplishments, drugs eligible for transdermal delivery must meet certain physical criteria and not require immediate absorption into the body. The specific requirements for delivery limit the type of drugs available and the market potential for this technology. Companies are now finding ways of expanding the portfolio and opening up new markets through development of new passive technologies, and more importantly, through development of active patches that utilize an external energy source.

PASSIVE PATCHES CREATED THE MARKET BUT HAVE LIMITED POTENTIAL

There are multiple indications presently associated with transdermal delivery, such as hormone replacement therapy, contraception, and pain management, but targeting only these indications and applications severely limits the market potential for transdermal drug delivery. Passive patches have advanced in technological capabilities and are now being used to target other indications, such as central nervous system disorders. The DOT Matrix technology developed by Noven Pharmaceuticals revolutionized passive transdermal delivery and enabled patches to become smaller in size with better adhesion characteristics. The patch's unique concept of storing the drug in an acrylic mix and using a thin layer of silicone to provide adhesion allowed for the storage of additional drug and provided the technology for the first estrogen/progestin combination patch. Noven Pharmaceuticals is developing this patch for many other indications and recently launched Daytrana, a patch based on DOT Matrix technology (Figure 1) for the treatment of Attention Deficit Hyperactivity Disorder. The improvements in passive patch technology are leading to development of more small molecules for transdermal drug delivery, but they are still limited to developing compounds within a narrow range of physical characteristics.

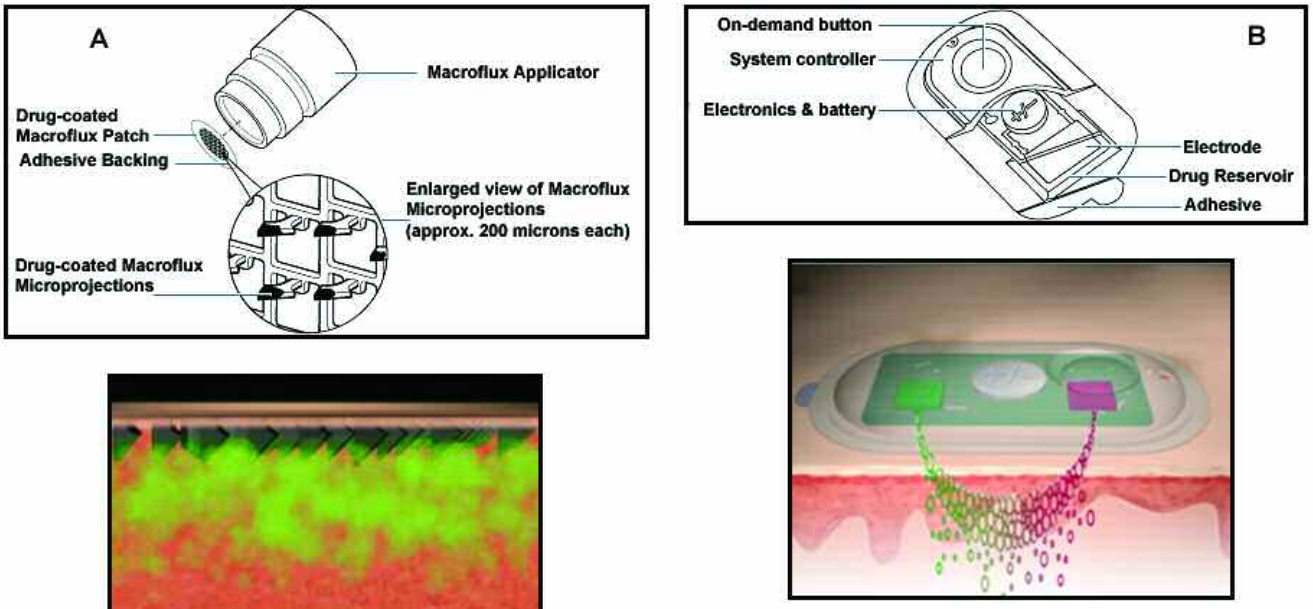
Some companies are attempting to expand the capabilities of passive patches by eliminating the use of the skin as the rate-controlling membrane. Bypassing the stratum corneum allows for the delivery of larger molecules with properties uncharacteristic of typical transdermal drugs. Alza Corporation has developed a device, Macroflux (Figure 2A), which delivers

FIGURE 1



The circular image is a digital photograph of the adhesive layer of a DOT Matrix® patch taken with a scanning electron microscope.

FIGURE 2



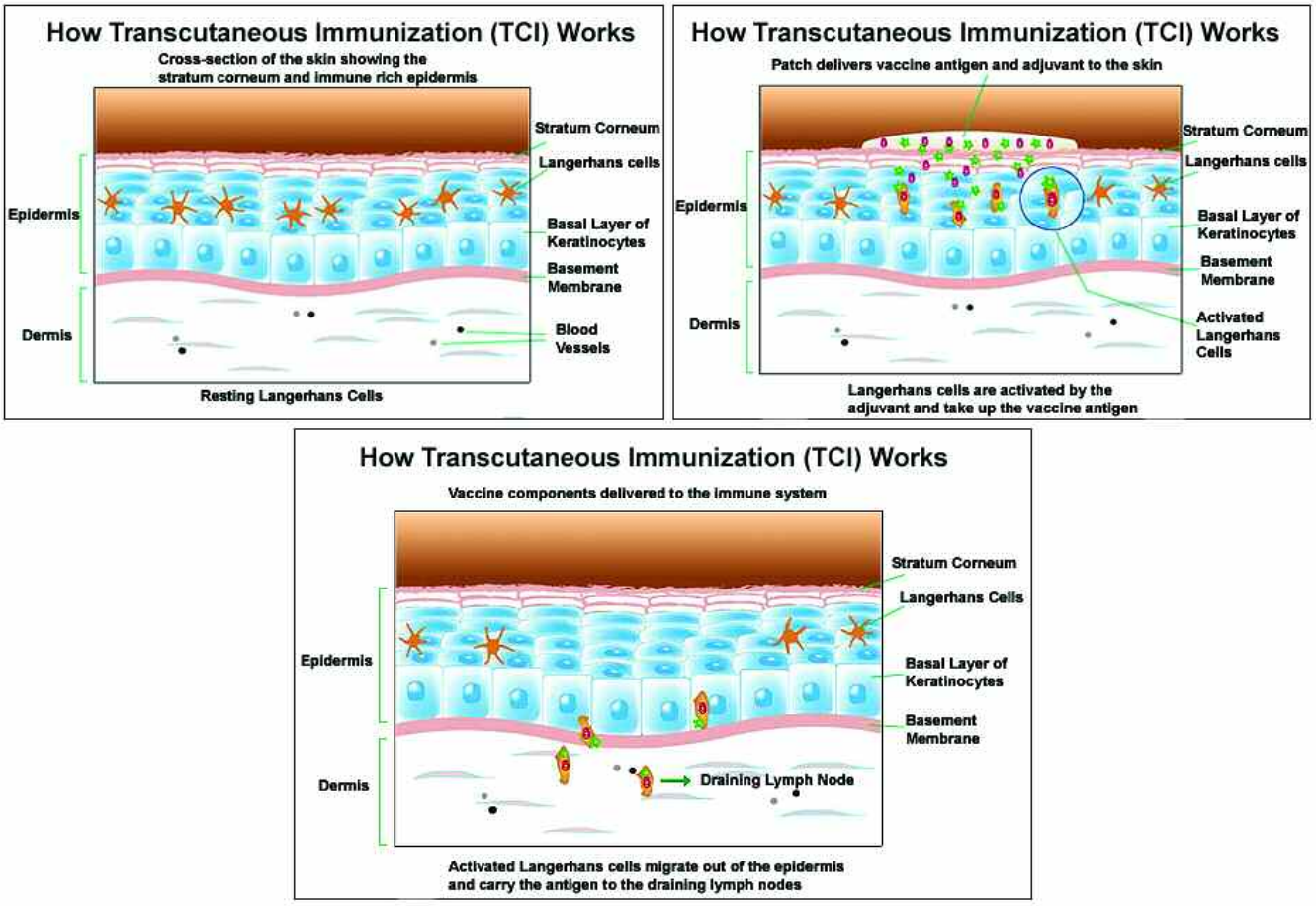
A) Macroflux® technology is designed to enable painless convenient patient administration of therapeutic proteins and vaccines. B) E-TRANS® electrotransport technology enables patient-controlled, pulsatile, and macromolecule delivery through intact skin.

a patch with microprojections on it that extend through the stratum corneum. The projections, ranging from 125 to 175 microns in length, extend past the stratum corneum but do not reach the layers of skin with nerves. The patch causes no pain to the patient, and the mechanism for which the patch is applied can be reused. This method is only ideal for potent drugs, as only 100 micrograms of a compound can be delivered, but it is seen as a potential application for vaccinations. Iomai Corporation is another company seeking to bypass the stratum corneum, but it is accomplishing that with a slight abrasion before patch application. Iomai's Transcutaneous Immunization (TCI) technology (Figure 3) is being developed for vaccination of several diseases, including travelers' diarrhea and anthrax. The system uses a device to remove the stratum corneum through a mild abrasion and then places the patch over the area for 1 to 6 hours. The patch contains an adjuvant LT toxin and disease antigen that work together for activation of the Langerhan's cells. These cells then travel to the lymph nodes where the immunization process takes place. Both technologies circumvent the stratum corneum but still have limitations due to the physical constraints of the molecules capable of delivery and the slight abrasive nature of the methods.

NEW APPROVALS INTRODUCE ACTIVE DELIVERY TO THE MARKET

The active patch delivery era commenced June 2006 with the launch of Synera, a topical patch from Endo Pharmaceuticals and ZARS Pharma. The lidocaine/tetracaine patch is approved for use as local dermal analgesia for superficial venous access and dermatological procedures. Topical lidocaine has been on the market for years, but Synera differs because of the active delivery system it utilizes. ZARS

FIGURE 3



Transcutaneous immunization (TCI) is a new method of vaccination that utilizes the skin. TCI represents a novel combination utilizing established knowledge relating to skin penetration, the potency of adjuvant-based immunostimulation, and data showing that Langerhans cells are highly desirable targets due to their antigen-presenting cell function.

Pharma developed the Controlled Heat-Assisted Drug Delivery (CHADD) technology (Figure 4) to help speed up absorption of the product through heat admission. The technology consists of a pouch filled with a proprietary compound that heats up when exposed to oxygen, and for Synera, the heat admission is approximately 30 minutes. The CHADD technology offers flexibility and can be designed for delivery of heat for up to several hours. ZARS Pharma is currently developing this patch further in different combinations with other topical and systemically delivered drugs.

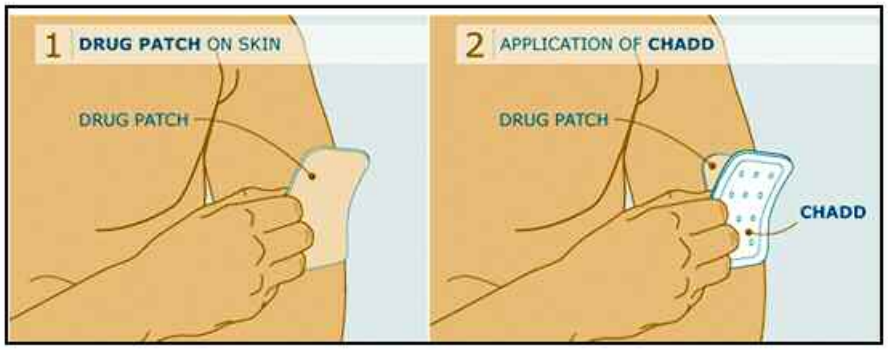
The second active patch delivery system expected to enter the market uses the E-TRANS® (Figure 2B) technology from Johnson & Johnson, developed by their transdermal technology company, Alza Corporation. The E-TRANS fentanyl patch was approved in May 2006 but is not expected to enter the market

until early 2007. E-TRANS utilizes electrotransport technology through emission of low-level electrical current. The energy applied allows for fentanyl to quickly enter the body with a similar pharmacokinetic profile to IV-based fentanyl infusion. The most appealing and exciting aspect of this technology is the ability for self-dosing. The patient controls the dose by pushing a button to release the electrical energy, providing similar control to that of an invasive patient-controlled IV pump. In preclinical studies, the device has shown the capability of delivering compounds over 25,000 daltons, making protein delivery a potential application of this technology.

COMPANIES DEVELOPING NEW TECHNOLOGIES WITH BROAD CLINICAL APPLICATIONS

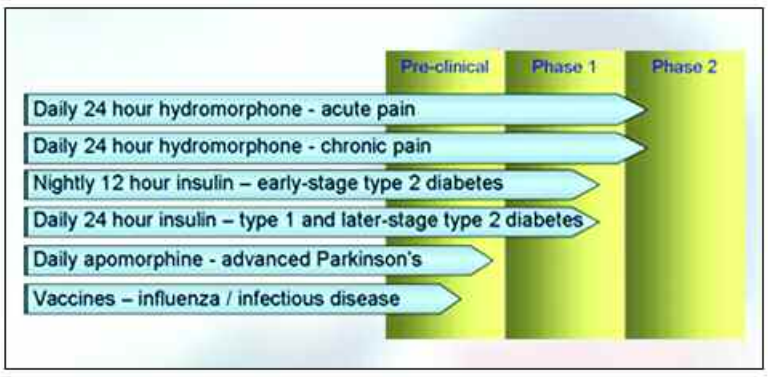
Altea Therapeutics is developing an active patch capable of delivering compounds over 500 daltons as well as water-soluble drugs. The PassPort technology utilizes rapid bursts of thermal energy to open up microchannels in the skin that bypass the stratum corneum. The technology has a wide array of applications (Figure 5) and is capable of delivering bolus levels, sustained release, and vaccine delivery. The PassPort patch consists of a drug reservoir and screen containing wafer-thin metallic filaments. The application process requires a small hand-held battery device that is used to create the active energy needed for the creation of the microchannels. The patch is attached to the applicator with the metallic screen side of the patch applied to the skin and activated with a click of a button, creating the rapid bursts of thermal energy. This painless process only requires milliseconds and is presently being designed to remain on the skin for up to 24 hours. Once the patch is removed, the microchannels immediately close, returning to the state prior to application. This system shows promise and is in clinical trials for delivery of opioid pain products, insulin, and vaccines. One of the benefits to this

FIGURE 4



CHADD® is a disposable, self-adhesive heating unit that generates heat when exposed to oxygen in the ambient air. The CHADD unit consists of a powder-filled pouch laminated between a top cover film with oxygen-regulating holes and a bottom film with a pressure-sensitive adhesive layer. The heat-generating powder consists of a proprietary chemical mixture.

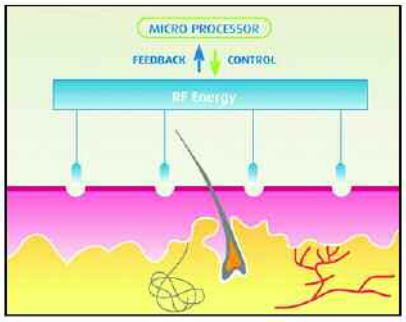
FIGURE 5



Altea's PassPort® patch opens the way for many more drugs and vaccines to be delivered painlessly via the skin as seen from its pipeline chart.

TRANSDERMAL MARKET

FIGURE 6



TransPharma has applied well-proven RF Technology commonly used in minimally invasive surgery, such as laparoscopic procedures, to create RF-MicroChannels in the skin surface. Each of these RF MicroChannels is of precise dimension to enable reproducible delivery of molecules via a specially formulated patch.

technology is the elimination of heat as a complication because the microchannels eliminate the use of skin as a rate-limiting membrane. Most passive patches rely on the skin as a transfer point of the drug, and when the skin heats up, absorption also increases, which can lead to deadly consequences. Additionally, the company's polymer system enables use of approximately 90% of the drug, helping reduce manufacturing cost and reducing the possibility of abuse in opioid drugs.

TransPharma Medical is developing its own proprietary system that also utilizes the formation of microchannels for transdermal delivery. The ViaDerm system uses radio frequency technology (Figure 6) to create channels in the skin via skin ablation of the stratum corneum. These channels can be 50 microns in diameter, big enough for the largest drug molecules to enter and are stable for up to 24 hours. TransPharma Medical uses a hand-held battery-operated device to create the radiofrequency needed for formation of the microchannels. Through this device and its feedback system, the ViaDerm system can custom create the depth and number of microchannels needed depending on the drug to be delivered and the individual's skin type. These controls make the device safe for human use as well as providing a valuable and accurate transdermal delivery mechanism. The system is capable of delivering a variety of hydrophilic and large molecular weight compounds, but TransPharma Medical is currently focusing on delivery of proteins, specifically parathyroid hormone (PTH) and an undisclosed protein. The protein is placed on the patch in dry powder form and relies on the interstitial fluid, created from the microchannels, to dissolve it and allow for systemic delivery.

SUMMARY

Transdermal drug delivery is still a relatively new field in the pharmaceutical market. The first drugs to utilize patches were of simple design and did not yield much technological creativity until the mid-1990s. Despite the progress in passive patch design, they are only able to adequately deliver small molecular weight compounds with favorable physical properties. Advanced transdermal drug delivery through utilization of an external energy source is now beginning to overcome many of these challenges with potential market availability in 5 years. Once thought to be impossible, active patches are proving they are capable of delivering proteins and providing an alternative to needle delivery, much to the desire of patients and physicians.

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.

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DRUG DELIVERY Executive

Egalet

EGALET: A WORLD LEADER IN EROSION-BASED THERAPEUTICS

Egalet's leadership position in erosion-based, controlled-release technology has fostered the development of a product pipeline that currently has four products in clinical trials. The two leading products are about to enter late-stage pivotal studies in the cardiovascular and pain markets. In addition to its erosion technology, Egalet®, which can be used for almost any pharmaceutical, the company has also developed Parvulet®, a novel approach for pediatric drug delivery that combines taste-masking with easy-to-swallow characteristics. Following the closing of a major venture financing round, Egalet now intends to leverage its first-class delivery, formulation, and manufacturing expertise through additional internal product development programs as well as licensing arrangements. Drug Delivery Technology recently interviewed Dr. Jan Quistgaard, CEO of Egalet, to discuss the exciting opportunities offered by erosion technology and the advantages this innovative approach possesses.

Dr. Jan Quistgaard
Chief Executive Officer
Egalet

"Each of our technologies offers potential partners unique benefits, so whether they are looking to improve bioavailability, decrease the number of tablets that need to be taken a day, or deliver active drug at a specific time, we are able to provide innovative solutions. All have one thing in common – a goal to improve the lives of patients."

Q: What are the origins of Egalet and when was the company founded?

A: Egalet, the company and technology, really have their origins with Daniel Bar-Shalom. As a pharmacist, Daniel appreciated the need for better, more patient-friendly drugs. The company was founded in 1995 as BM Research based on a delivery idea that Daniel had. Through seed investment from QueQuoin Holdings, the delivery idea was developed into a working concept, including developing the manufacturing process around injection moulding. This process took about 5 years and involved changing the name of the company to Egalet. In 2001, we attracted DKK 106.9 million in funding from a consortium of Scandinavian investors. These proceeds facilitated further optimization of the technology and manufacturing process. We then began to develop our product pipeline and initiate collaborations. Earlier this year, we secured significant funding from investors co-led by Atlas Venture and Index Ventures of DKK 173 million. We are now on track to take our lead products to commercialization, and an IPO remains an option in the future, but we and our investors are not averse to other exit options, such as an M&A.

Q: Explain your erosion-based technology and why it is so unique.

A: The Egalet® technology is one of the first to use erosion rather than the more common diffusion technique. The medicine is incorporated into a matrix tablet that is gradually eroded at a

constant speed. We currently have two versions of the Egalet® tablets, a two- compartment version that allows constant erosion and a formulation that includes a lag compartment. This tablet allows timed release of the medicine and enters the realms of a new area in pharmaceuticals termed chronotherapeutics.

Q: What is the Parvulet® technology?

A: With the Parvulet® technology, Egalet® has created a universal formulation that is acceptable for all children. Drugs contained in this formulation are dispensed as a special dry powder or tablet that on exposure to a small amount of water turns into a tasty, soft textured, "pudding-like" mass. The formulated drug can be incorporated into a familiar carrier, such as a spoon, with the water being added just before administration. With governments around the world now putting considerable pressure on the pharmaceutical industry to improve the availability of improved medicines for children, the use of better delivery systems could prove a cost-effective and safe way to improve compliance in this underserved and neglected market.

Q: What products are you currently developing?

A: Egalet's lead product, which is about to enter Phase III trials, is a constant-release Egalet® formulation of an undisclosed cardiovascular drug for the treatment of hypertension. This formulation enables once-daily administration rather than twice-daily used in currently available tablet forms.

Our second product in late-stage development is a constant-release Egalet® formulation of morphine that uses a special polymeric formulation. This tablet cannot be crushed or melted so it is resistant to abuse, a particular advantage considering the FDA's strict regulation of opioid-based drugs' potential for abuse. Our morphine product is also not subject to dose-dumping if taken at the same time as alcohol.

Q: Tell us more about your manufacturing process for the Egalet® technology, it's unusual for the pharmaceutical industry, isn't it?

A: We understand that we are the first to introduce the same injection-moulding technique used in the plastics industry to pharmaceuticals. Injection moulding means that tablets can be produced quicker and with less variation in size compared to conventional tablet manufacturing. Our manufacturing process also allows the size and composition of Egalet® tablets to be varied between batches, while permitting very little variation within each batch.

Q: What partnership do you currently have and what makes Egalet® attractive to several other potential partners?

A: We currently have an agreement with the Consumer Healthcare Division of GlaxoSmithKline to develop an oral, erosion-based formulation of an undisclosed OTC medicine using our timed-release Egalet® technology. At present, we are in negotiations with several other potential partners.

Here at Egalet®, we offer a comprehensive suite of services from formulation to manufacturing. Each of our technologies offers potential partners unique benefits, so whether they are looking to improve bioavailability, decrease the number of tablets that need to be taken a day, or deliver active drug at a specific time, we are able to provide innovative solutions. All have one thing in common – a goal to improve the lives of patients.

Q: What are the company's long-term goals?

A: We believe our innovative products and technologies provide us with the foundations for a successful future. We intend to build a broad pipeline of erosion-based products, initially focusing in the pain and cardiovascular markets. As a private company, we ultimately believe that a public offering in the form of an IPO will provide us with the necessary capital to realize our goals. The significant funding in the round co-led by Atlas Venture and Index Ventures in March 2006 has certainly put us on the right track. With these proceeds and favorable market conditions, an IPO certainly remains an option in the future as well as the right M&A. ◆

Drug Delivery Showcase

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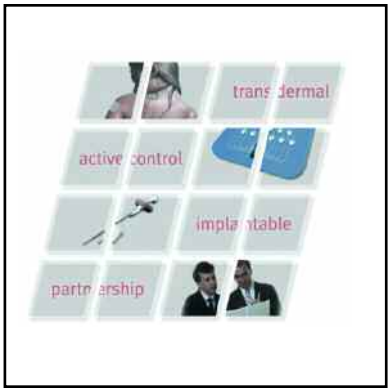
Multiple Platforms & Products

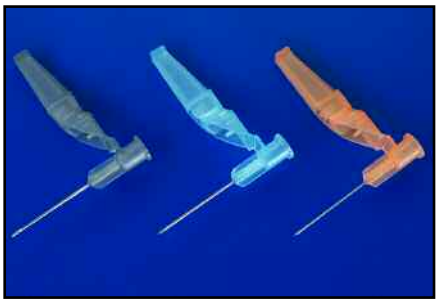


Novosis AG is a pharmaceutical company dedicated to development and manufacturing of dermal, transdermal, and implantable drug delivery systems. Novosis has developed proprietary and patented technologies for actively controlled and non-continuous drug release. Big international pharmaceutical customers rely on the partnership with Novosis based on creative solutions and the successful integration of pharmaceutical development and GMP-manufacturing. Novosis AG is also developing own proprietary products and thus providing licensing opportunities for partners interested in transdermal and implantable application systems. For more information, visit Novosis at **www.novosis.com.**

Sensor Technology

CMOSens (see-mo-sens): is a basic technology that is setting standards for high-precision sensor systems. Merging a semiconductor chip (CMOS) with sensor technology makes it possible to achieve highly integrated system solutions characterized by excellent sensor precision, digital intelligence, and reliability. The sensor component, amplifier, and A/D converter form a single unit on the same silicon chip. The digital intelligence of the CMOSens sensor facilitates output of a fully calibrated, temperature-compensated signal. The integral CMOSens "intelligence" of the chip thus allows measurement data to be output using a standard digital interface, such as SPI, for extremely straightforward processing. Due to a compact single-chip design, sensors based on CMOSens Technology have excellent resistance to electromagnetic interference (EMC), which is a significant technical advantage of this highly modern sensor technology. For more information, visit Sensirion, Inc. at **www.sensirion.com**.

Needle Safety Device



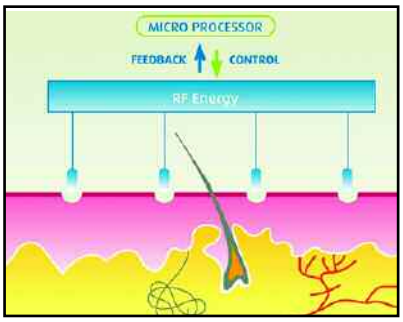
Smiths Medical has long been a leader in the innovation of needle safety devices that meet clinical expectations and provide a cost-effective, safety-engineered solution to needle safety requirements. Today's hospital and federal directives demand accuracy, efficiency, cost-saving measures, as well as patient and healthcare worker safety, all within an increasingly fast-paced clinical environment. Smiths Medical has responded to these needs by advancing its Hypodermic Needle-Pro® needle-safety device to incorporate features that give the clinician an important edge when it comes to safety, convenience, and cost-efficiency. For more information, contact Smiths Medical at (800) 258-5361 or visit **www.smiths-medical.com**.

Drug Delivery Showcase

Needle-Free Epidermal Delivery

PowderMed's ground-breaking approach employs a proprietary technology platform called PMED (Particle Mediated Epidermal Delivery), which relies on pressurized helium to shoot DNA-coated gold microparticles at 1,500 miles per hour into the immune network of the skin, which is impossible to access using a needle and syringe. The targeting of this immune cell rich tissue means that immune responses are seen with very small (microgram) doses of DNA; 1,000-fold less than with intramuscular DNA injection. The PMED "gene gun" requires minimal medical training, allows self-administration,and requires no refrigeration for stockpiling. PowderMed's lead product is a DNA-based prophylactic vaccine to target annual and pandemic influenza, which has successfully completed Phase I trials. For more information, visit PowedrMed at **www.powdermed.com**.

Cell Ablation Technology



TransPharma Medical has applied well-proven RF Technology commonly used in minimally invasive surgery, such as laparoscopic procedures, to create RF MicroChannels in the skin surface. Each of these RF MicroChannels is of precise dimension to enable reproducible delivery of molecules via a specially formulated patch. RF-MicroChannel drug delivery is ideally suited for drugs that must be injected, as well as for a variety of orally delivered drugs with poor bioavailability. These include polypeptides and other large molecules, small molecules (including existing transdermal drugs), regional and topical applications, and enhanced immunization programs. TransPharma has adapted and modified the RF Cell Ablation Technology to enable the creation of precise RF-MicroChannels on the skin surface in a highly controllable manner. For more information, visit **www.transpharma-medical.com**.

Metering Delivery Devices

Rexam Pharma is a leading specialist in drug delivery devices and primary pharma packaging. The company has a recognized expertise in a wealth of different areas, including inhalation devices, such as dry powder inhalers and valves for pressurized metered dose inhalers; metering pumps and airless systems for topical or transdermal gels; spray pumps for topical or systemic use via the nasal or the buccal and sublingual routes; and injectors and implanters. With comprehensive resources in innovation, development, and industrialization and full GMP manufacturing, Rexam Pharma stands out as a partner of choice. For more information, contact Rexam Pharma at (914) 640-1310; mailboxpharma@rexam.com or visit **www.rexam.com/pharma**.

Manufacturer & API Specialist

Hovione is a fine chemicals company that specializes in the process development and manufacture of active pharmaceutical ingredients and regulated intermediates. Dedicated to solving the problems associated with the industrial production of complex chemical entities, the company's expertise in process chemistry and regulatory compliance to cGMP standards is based on more than 40 years of experience. Over that time, its ability to provide customers with timely solutions that are dependable and economical has given them a worldwide reputation for superior customer service. Hovione's business is 50% custom synthesis for large pharma and biotech companies and 50% generic products. More than half of today's sales consists of products launched less than 5 years ago. For more information, visit Hovione at **www.hovione.com**.

SUPERCRITICAL FLUID

New Enabling Technologies for Drug Delivery

By: Pratibhash Chattopadhyay, PhD and Boris Y. Shekunov, PhD

Cost-Effective, Environmentally Friendly Supercritical Fluid-Based Particle Engineering Technologies Meet New Drug Delivery Challenges & Offer New Life for Mature Drugs

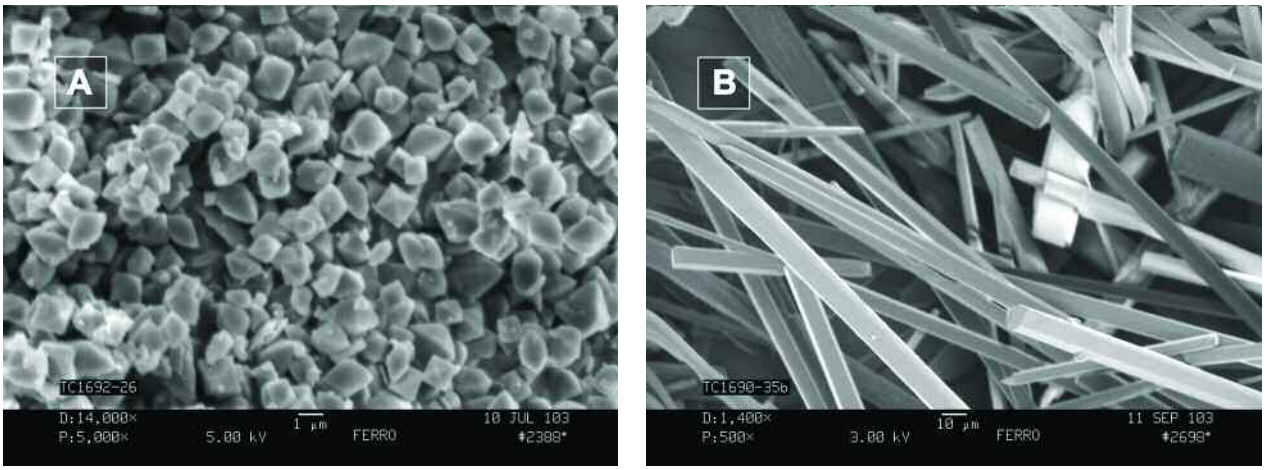
INTRODUCTION

Whether developing new clinical compounds or seeking new intellectual property rights for patent extensions, pharmaceutical companies are exploring advanced manufacturing processes to enable their products to take advantage of new or modified routes of administration. New therapeutic applications, increasing requirements for efficacy and safety, and challenges presented by new classes of drugs call for new particle processing technologies. Additional needs include better quality control over particulate and solid-state properties, improved economics and batch consistency, and the means to produce enhanced formulations not commonly achievable via more conventional methods.

Successful feasibility studies are demonstrating the ability of supercritical fluid (SCF) technologies to effectively meet these pharmaceutical processing needs. Novel SCF technologies give drug developers unprecedented particle engineering abilities to control the size, type, and morphology of drug particles. These scalable continuous or batch processes are environmentally friendly, require "mild" operating conditions, and provide an enclosed, sterile processing environment. Unlike conventional technologies that utilize large volumes of organic solvent for processing, these technologies use low-cost supercritical CO_2. Organic solvents dissolved in the supercritical fluid can be recovered and recycled by depressurization, producing virtually no waste stream – reducing environmental costs.

No single SCF process can realistically address all particle engineering needs. Because each drug and delivery system requires different physical characteristics and parameters, SCF technology must be applied in different ways to achieve specific results. At present, the authors have worked with four patented processes that produce nano- and microparticles with a narrow size distribution and consistent morphology. Two of these, Supercritical Fluid Extraction of Emulsion (SFEE) and Spray Freeze

FIGURE 1A and 1B



Morphology of the griseofulvin (GF) crystals produced using SFEE method: volume-weighted mean diameter (VMD) = 978 nm, number-weighted mean diameter (NMD) = 784 nm in comparison with (b) crystals produced using supercritical antisolvent precipitation under the same conditions of pressure, temperature, and solution flow rate.[1]

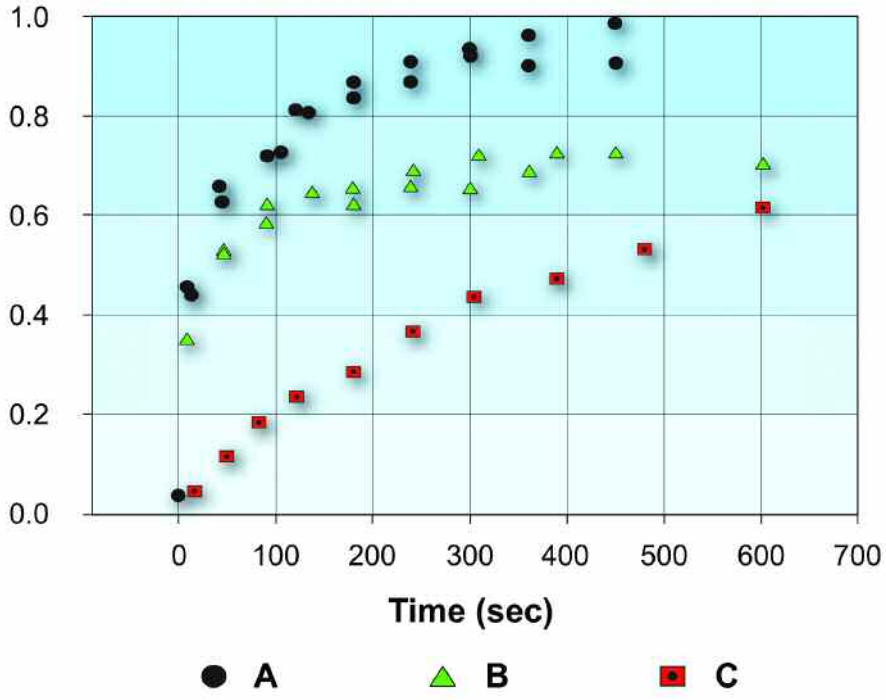
Drying (SFD), have exhibited notable success in meeting specific challenges to produce drug particles that are suitable for parenteral or respiratory drug delivery. These processes and a few applications that experience increasing marketplace demand are discussed here.

PARTICLE ENGINEERING FOR PARENTERAL DRUG DELIVERY

Approximately 40% of all drugs are poorly soluble in water, including many new drug molecules. Of particular importance are some of the small-molecule drugs currently in clinical development. Administration of such drugs presents a significant challenge due to their low bioavailability, high toxicity, and irregular absorption in the gastrointestinal tract.[1]

Formulating these materials into nanoparticles effectively alleviates these challenges by increasing surface area and enhancing the dissolution rate. However, current approaches in commercial use for production of nanoparticles have limitations. Micronization techniques, such as wet milling or high-pressure homogenization, have difficulty in reducing size below certain limits for most pharmaceuticals and expose the materials to possible contamination with grinding media. Adverse effects of high shear and temperatures also pose risks to the chemical and physical stability of the pharmaceutical compound.[2] All precipitation methods are challenged by the fact that most small-molecule drugs tend to form relatively large crystals. In addition, purity control and toxicity issues restrict the use of excipients and other additives designed to inhibit crystal growth. Oil-in-water (o/w) emulsion-based processes certainly offer enhancements in particle size reduction and more flexibility in achieving objectives related to shape, crystallinity, and surface properties. Unfortunately, these techniques are limited by several factors that make them unsuitable for large-scale production, such as emulsion instability during processing, high residual solvent content in the final product, and long processing times. Another drawback of traditional o/w emulsion-based processes is the potential for inconsistent particle size due to crystal growth (ripening) and agglomeration.[1]

FIGURE 2



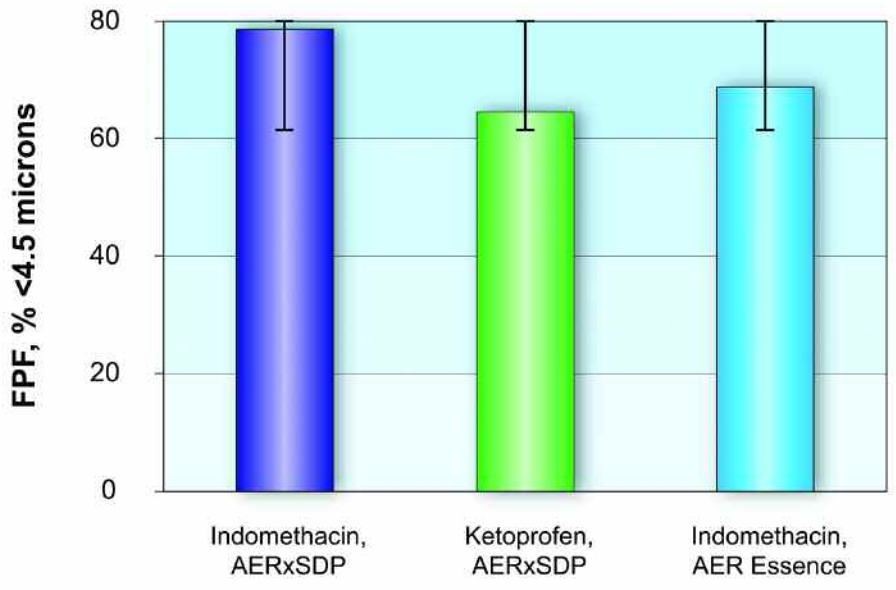
Dissolution profiles of two griseofulvin (GF) suspensions with (a) VMD = 760 nm and NMD = 224 nm (b) VMD 978 nm and NMD 784 nm compared with a micronized material with (c) VMD = 5.9 microns, NMD = 2.3 microns.[1]

SUPERCRITICAL FLUID EXTRACTION OF EMULSIONS (SFEE) FOR WATER-INSOLUBLE DRUG NANOPARTICLES

The SFEE method is based on extraction of the organic phase of o/w or multiple emulsions using supercritical CO_2. It combines the flexibility of particle engineering as offered by various emulsion systems with the efficacy of large-scale, continuous extraction using SCF. In doing so, SFEE effectively overcomes the limitations of conventional techniques with respect to the control of particle size distribution and morphology, process scalability, processing times, reduction of residual solvents in the final product, waste streams, and particle collection. There is a fundamental difference between the SFEE process and any antisolvent precipitation (supercritical or liquid) from a homogeneous solution. In the precipitation from solution, the particles are nucleated and grow within the whole solution volume. Therefore, the size of particles produced depends on the supersaturation during mixing and on the nucleation and growth constants, which are difficult to control. In the SFEE process, the nucleation and growth are confined by the aqueous phase and therefore localized within the droplets, with some limited interaction between the droplets. As a result, the particle size obtained in SFEE is typically smaller by an order of magnitude than those produced during solution precipitation.[1]

The precipitation process in SFEE occurs relatively slowly, providing the opportunity to obtain thermodynamically stable solid structures of a drug or drug-excipient mixture. Coating or encapsulation of active ingredients

FIGURE 3



Fine particle fraction (FPF) of different lipid-drug particles obtained using the AERx® SDP and Essence™ Systems.[5]

is also more efficient in such a process, as precipitation of composite particles is confined within the emulsion droplet volume. The dissolution of CO_2 in some biodegradable polymers followed by gas expansion in the suspension can lead to porous or hollow structures useful for some formulations. SFEE is a truly continuous process, and can provide products in the form of solvent-free aqueous suspensions with solid content between 0.5% and 10%. Surfactants, which are commonly used as pharmaceutical excipients, are retained in the aqueous phase of the suspension. More highly concentrated suspensions as well as pure dry powders can be obtained by using high-pressure in-line filtration or SFD.[3]

Finally, SFEE has been shown to be simpler, less bulky, and more efficient than most spray-drying or vacuum-drying equipment. The equipment used in the SFEE process includes a standard extraction column that is made of inexpensive stainless-steel tubing, and produces a continuous flow of the product (suspensions) at a relatively large flow rate. Carbon dioxide is an inexpensive solvent and can be easily recycled, if necessary, in an enclosed and economical process.[1]

The water-insoluble antifungal agent griseofulvin (GF) was chosen as a model drug in one feasibility study for SFEE. GF exhibits a persistent acicular morphology and difficulties in size reduction using conventional SCF antisolvent precipitation techniques. Figure 1 presents the micrographs of different particles obtained using SFEE (Figure 1a) and particles obtained using a conventional supercritical antisolvent (SAS) precipitation technique according to the method described in another study.[4] The pressure, temperature, and solution flow rate were the same for both the SFEE and SAS methods, therefore these experiments are representative of the different mechanisms of particle formation afforded by supercritical fluid extraction and antisolvent precipitation. Figure 1 shows that substantial difference is observed in the particle size and shape. It is very characteristic for the SAS process to attain the acicular morphology with the longest crystal dimensions between 20 and 200 microns and volume-weighted mean diameters (VMD) above 10 microns. In contrast, the SFEE process produced prismatic crystals with VMD typically between 0.5 and 1 microns. Thus, the tenfold reduction in the particle size and production of uniform non-agglomerated GF particles with a small aspect ratio were achieved using SFEE. All of the particles produced were crystalline.[1]

One of the main objectives of producing nanosuspensions is to increase the bioavailability of drugs with poor aqueous solubility. The dissolution rate for the GF suspensions (Figure 2) depended on the particle size. Compared to the reference material, the dissolution rate increased by the factors 2 and 4 during the first 4 minutes for VMD = 980 nm and 760 nm, respectively. Nearly 100% of the drug was dissolved within a period of 8 minutes.[1]

It should be noted that all materials produced using SFEE indicated a high degree of crystallinity. This compares favorably, in terms of the physical stability, with the amorphous materials often obtained by milling, solubilization, or rapid precipitation techniques. The aqueous nanosuspensions also indicated a high degree of stability with respect to particle size changes.[1]

PARTICLE ENGINEERING FOR PULMONARY DELIVERY

A key target for pharmaceutical research is the development of drugs to treat diseases, such as diabetes, asthma, cystic fibrosis, and chronic obstructive pulmonary disease, using the respiratory route for administration. Micronized particles typically produced by jet-milling are the main formulation component in pressurized metered dose inhalers (pMDIs) and dry powder inhalers (DPIs). However, mechanical micronization provides only limited control over particle size and powder crystallinity, and has detrimental effects on powder cohesiveness and flow properties. Recent trends in inhalation therapy call for alternative particle engineering technologies, namely: (1) development of high-potency compounds requiring accurate and consistent doses delivered to the lung; emerging systemic delivery via the pulmonary route; (2) delivery of therapeutic proteins and other biomolecules

with new adsorption mechanisms; (3) new controlled-release approaches; and (4) an ever-growing requirement for more efficient inhalation devices.[3]

SFEE FOR PULMONARY DRUG DELIVERY

For both topical and systemic administration of drug through the pulmonary route, nanoparticulate formulations (typically in the 100 to 700-nm range) offer several important advantages when compared to more traditional microparticles (1 to 5 microns). Some examples include bioavailability enhancement, higher delivered dose, and better dose uniformity. In addition to the delivery of drugs for immediate release, another rapidly developing area of interest is the composite drug-carrier systems for respiratory delivery. The challenge of using the polymeric colloidal drug carriers due to potential clearance/toxicity issues has stimulated current research into pursuing alternative lipid carriers, such as liposomes, lipid emulsions, lipid complexes, and solid lipid nanoparticles (SLN). Although the role of lipids for respiratory delivery has yet to be assessed, their toxicological profile is expected to be better than for polymeric systems due to the lack of parenteral side effects. It is feasible that aqueous suspensions and perhaps dry powder formulations of SLN can be used for pulmonary administration of drugs. A feasibility study examined model drug-lipid systems produced by SFEE, and tested these formulations using Aradigm Corporation's liquid inhaler platforms.[5] The model drugs were all non-steroidal anti-inflammatory agents. For this class of drugs, effective respiratory administration would benefit patients by eliminating gastrointestinal risks associated with long-term use.

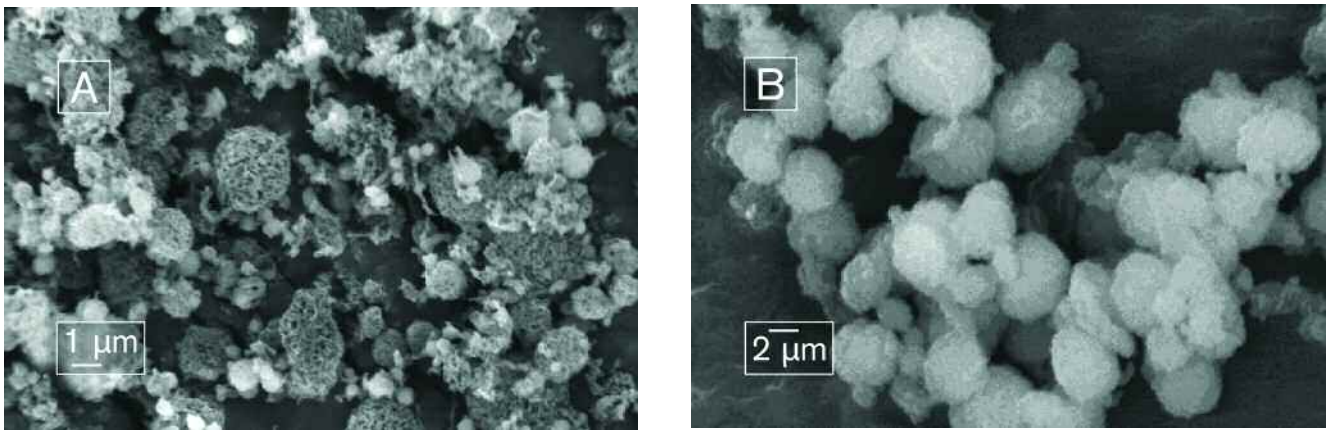
The SFEE method allowed for production of stable particulate suspensions of a narrow size distribution, with a volume mean diameter below 30 nm (D99 cumulative volume below 100 nm). The particle sizes obtained were significantly smaller than previously achieved by any other technique. The residual solvent content in the final suspension was consistently well below the permissible limits. Stable drug loading values up to 10% (w/w) were obtained for indomethacin (IN) and 20% w/w for ketoprofen (KP). The lipid nanoparticles were crystalline and showed no change in the polymorphic form after processing, although widening of the X-ray diffraction (XRD) patterns and smaller fusion enthalpy/melting point indicated a significant decrease of the crystallinity due to the structural disordering and size effects. This analysis also showed no presence of the crystalline drug phase in the nanoparticles, up to the stability limit for each drug.[5]

In the aerosol analysis, very high effective dose (ED) recoveries were observed for all lots of suspension formulations, with means ranging between 55% and 60% when using the AERx® Single Dose Platform (SDP) and approximately 50% when using the AERx Essence™ system. The aerosol fine particle fraction (Figure 3) is consistent with delivery of most of the aerosol to the deep lung. It was demonstrated that SFEE is a viable new method for the production of drug-lipid formulations.[5]

SPRAY FREEZE DRYING (SFD) FOR PULMONARY DRUG DELIVERY

Spray freeze drying with compressed CO_2 (SFD) provides a consistent method for particle production of water-soluble drugs. In particular, this technique is well-suited to production of particulate forms of biomolecules with excipients within the respirable size range. The method is based on the principle whereby aqueous solutions of biomolecules and additives are simultaneously atomized and frozen by mixing and subsequent expansion through a nozzle with liquid or supercritical CO_2. The frozen solvent is then removed either by vacuum or atmospheric freeze-drying. Some organic

FIGURE 4A and 4B



Particle morphology of pure insulin at (a) 0.5% w/w and (b) 5% w/w solute concentration.[9]

solvents and o/w emulsions can also be used in this method to produce particles of water-insoluble drugs or composite materials. The SFD technique is able to produce powders of both low bulk density (< 0.1 g/cm^3) and particulate density (< 0.5 g/cm^3), often also with a large aerodynamic shape factor (χ > 2). These characteristics lead to enhanced particle dispersion and possibility for deep-lung deposition. In addition, the porous and homogeneous powder bed facilitates sublimation, which in turn can be improved several-fold compared to traditional freeze-drying.[3] SFD is the closest to the standard lyophilization process in terms of both freezing and drying temperatures, with the added dimension of particle size engineering and a greatly reduced process cycle, where the freezing is accomplished in 10 to 100 microseconds.[6] It is also simpler and more efficient than spray-freeze-drying into liquid N_2, which has been successfully used to engineer different particles of proteins, peptides, and vaccines.[7,8]

A feasibility study used SFD to produce particles of the model compound, insulin, to explore suitability for administration by new DPIs, MDIs, and some types of liquid inhalers. Computational fluid dynamics showed that supercritical conditions before expansion are important to achieve smaller particle size and more uniform, narrower size distribution. It was shown that by using only two parameters — solute concentration and flow rate of the solution feed — the size and structure of insulin particles can be efficiently controlled in this process, with the most important being the total concentration of insulin and excipients in the solution.[6]

The products varied from relatively cohesive aggregates of nanoparticles with primary particle diameters of 100 to 300 nm at 0.5% w/w solution concentration, shown in Figure 4a, through platelet shapes to well-defined and easily dispersible spherical microparticles formed above 5% w/w solution concentration, shown in Figure 4b. The volume median and volume mean diameters measured for the aerosolized powder were between 1 to 3 microns for all products. Although the effect of different excipients on the insulin stability has yet to be assessed, different excipient combinations utilized thus far have not significantly affected particle size and suggest that these formulation issues can be addressed successfully. The SFD process is sufficiently robust to be utilized on a large scale and can consistently produce particles of biomolecules, such as proteins, peptides, and vaccines in the respiratory size range.[9]

CONCLUSIONS

SCF-based processes are not a single technique but rather a group of different technologies, each involving different physical principles, applicable to different molecules, and resulting in different products. While none of the individual techniques is universal, their complementary physical properties allow particle engineering and production of relatively pure physical forms as well as composite drug-excipient particles of various size, morphology, and structure.

The aforementioned processes can be scaled up for commercial manufacturing. These and other SCF technologies represent a "tool-box" to be tailored for specific applications, which can offer significant processing advantages, and in many cases, provide a viable economical alternative to the existing particle technologies. Additional feasibility studies for the next steps in commercial application are in progress, as well as an increasing number of initial studies to validate new opportunities.

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BIOGRAPHY

Dr. Pratibhash Chattopadhyay is a Senior Scientist at Ferro Corporation. He is a member of the team responsible for the development and commercialization of Ferro's particle engineering techniques using supercritical fluids for various drug delivery platforms. He earned his BS in Chemical Engineering from Anna University in 1997 and his PhD in Chemical Engineering from Auburn University in 2002. Since 2001, he has published 15 research papers, has 8 issued patents, and 34 patents pending.

Dr. Boris Shekunov is Director of Pharmaceutical Technology at Ferro Corporation, where he leads numerous R&D projects within the pharmaceutical industry. He earned his PhD in Physical and Mathematical Sciences from Moscow State University in 1991 and held positions in Physical Chemistry and Pharmaceutical Sciences at the University of Strathclyde, De Montfort University, and University of Bradford in the United Kingdom. He was awarded the EPSRC Advanced Research Fellowship in Process Engineering and was a Reader in Pharmaceutical Materials Science at the School of Pharmacy, University of Bradford. He also served as Head of the Particle Science Group at Bradford Particle Design Ltd (later part of Nektar Therapeutics Inc.).

BUCCAL DELIVERY

Buccal Delivery of Analgesics for Breakthrough Pain

By: Andrew L. Finn, PharmD

INTRODUCTION

The chronic pain market is growing, dynamic, complex, and full of opportunity. The market for treating chronic and acute pain is expected to rise from $15 billion in 2004 to $24 billion in 2008, according to a recent report by Decision Resources. Much of this growth is expected from the aging population and the introduction of novel systems for delivering existing pain drugs.

It is sometimes convenient to differentiate cancer pain from other types of severe or chronic pain. Approximately 4 million Americans suffer from some form of cancer, and 2.5 million of these have associated pain. The pain is frequently subdivided into two categories: background or underlying pain; and breakthrough pain. Approximately 1.5 million cancer patients face what is termed breakthrough pain (BTP) – intense pain episodes with rapid onset and variable duration.

In cancer patients, BTP is a significant medical problem that may bring on additional medical and quality of life conditions, such as anxiety, depression, and impairment in activity, mood, and sleep. BTP may be triggered by events, such as sneezing, coughing, and bodily movements, or may arise spontaneously. Patients typically experience between one and five breakthrough episodes per day, with time to peak severity, ranging from about 1 to 5 minutes. Although patients can sometimes predict onset of BTP, its sudden nature and rapid onset can disrupt normal activity.

A recent report by DataMonitor (Figure 1) states that fewer than half of all physicians who treat cancer follow scientifically based guidelines for treating pain. The obvious conclusion is that most cancer patients are receiving suboptimal pain relief.

Cancer is not the only condition associated with severe breakthrough pain. Individuals who have undergone trauma or major surgery, or with back and neck conditions, osteoarthritis, neuropathy/neuralgia, pancreatitis, fibromyalgia, and various gastrointestinal disorders may experience breakthrough pain for days to years at a time.

Immediate release (IR) morphine is the most common product used to treat BTP. However, no placebo-controlled studies have demonstrated IR morphine's effectiveness in managing BTP. Other opioids commonly used to treat BTP include oxycodone and hydrocodone, sometimes formulated with over-the-counter analgesics like acetaminophen. The connection between opioids and safe, effective treatment of BTP is complex and probably under-studied in the medical literature.

FENTANYL – THE IDEAL AGENT FOR BTP?

Among immediate-release opioids, fentanyl is widely recognized as the ideal agent given its potency (80 times that of morphine), rapid onset, and duration of effect. Fentanyl has a long history of safe use in cancer pain. Cephalon's Actiq® oral transmucosal fentanyl citrate (OTFC) product, launched in 1998, is still the only analgesic currently approved for treating BTP. Actiq is supplied as a lozenge that sits at the end of a disposable applicator. According to its label, Actiq is indicated for management of BTP in opioid-tolerant patients with cancer. Actiq has experienced a 36% compound annual growth rate in sales since 2002, and today generates about $500 million in revenues.

Clinical studies have demonstrated OTFC's superiority in treating BTP. In one report, OTFC was more effective than IR morphine in pain relief, and preferred by patients 16 to 1 over IR morphine.

Despite these impressive numbers and apparent superiority to IR morphine, Actiq appears to be infrequently used in breakthrough cancer pain, with less than 50,000 patients of the approximately 1.5 million Americans suffering cancer-related BTP actually using the product. This may be because of delivery system inconvenience, the cost or the manufacturer's ineffectiveness in raising the issue of proper pain management in the mind of busy clinicians, especially oncologists.

OTFC has limitations that include difficulty in dissolving the product in saliva. This may require that a patient suck and swab the buccal mucosa for up to 30 minutes to deliver the desired fentanyl dose. Alternatively, patients may use the higher strength versions to obtain relief and then have residual product left over.

Other oral transmucosal fentanyl products in development impose similar burdens on the patient. Cephalon's OraVescent® fentanyl tablet also requires that patients hold the product in their mouth, while the fentanyl dissolves in saliva and then diffuses through the buccal mucosa. The time for product dissolution may vary from dose to dose. Similar to OTFC, the absorption surface area and the time the product is in contact with that area are not controlled by the product. Irritation of the buccal mucosa by the product has also been reported in clinical trials.

BEMA DELIVERY SYSTEM

A novel fentanyl formulation, under development by BioDelivery Sciences International (BDSI), combines fentanyl's superior performance in treating BTP with 21st-century drug delivery technology. BDSI uses water-soluble, cellulosic polymers in its BEMA™ (BioErodable MucoAdhesive) drug

delivery system (Figure 2). The cellulosic polymers are formed into multilayered discs, with the layers having different properties and functions. Fentanyl is contained in the mucoadhesive layer of the disc, which adheres to the buccal mucosa within seconds after application. Fentanyl is completely dissolved in the mucoadhesive polymers and is available for mucosal diffusion immediately after moistening, without patient effort. The surface area of the disc is directly related to the dose of fentanyl administered, so it is not surprising that the product exhibits linear pharmacokinetics over a range of doses.

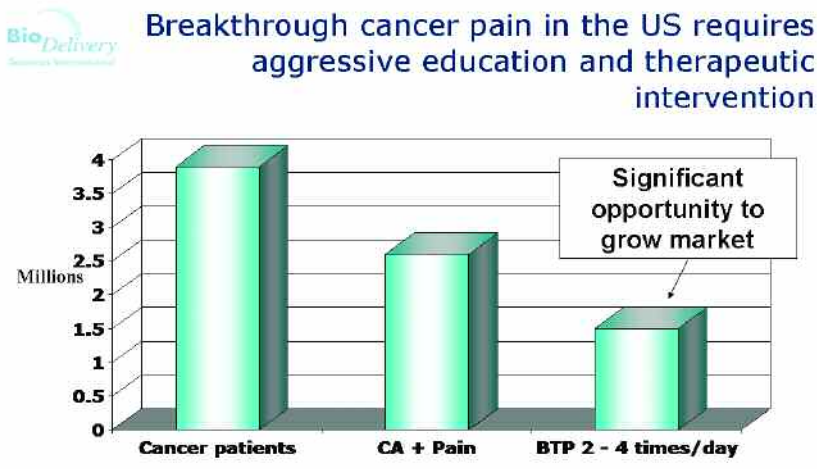
A second polymer layer, the backing layer, is added to the disc so that it is between the mucoadhesive layer and the interior of the mouth. The polymers used in the backing layer are also water soluble, but without mucoadhesive properties. The backing layer serves several functions, including preventing the disc from sticking to the teeth and acting as an occlusive barrier to prevent the fentanyl from diffusing out of the disc and into the saliva where it would be swallowed. Finally, the composition of polymers chosen for the backing layer defines the rate of dissolution of the layer, and in turn, the overall dissolution or residence time of the disc. Once the backing layer dissolves, the thinner mucoadhesive layer quickly dissolves. In the case of BEMA Fentanyl, the backing layer composition has been selected to provide a residence time (the time for fentanyl diffusion) of 20 to 30 minutes.

In contrast to other products, no effort is required on the part of the patient to hold the disc in place, move it around in the mouth or remove the product after the fentanyl dose is delivered. Further, there is no product residue remaining in the mouth after dosing and no residual product to dispose.

BEMA discs deliver a rapid, reliable dose of drug across mucous membranes for time-critical conditions like BTP.

BDSI licenses the BEMA drug delivery technology on a worldwide exclusive basis from Atrix Laboratories, Inc. (now a wholly-owned subsidiary of QLT Inc.).

FIGURE 1



BDSI's lead BEMA product, BEMA Fentanyl for breakthrough cancer pain, is currently in Phase III trials. Subsequent products in the BEMA system include a long-acting analgesic (BEMA LA) for a broader range of pain conditions, including chronic pain associated with osteoarthritis, lower back disorders, and neck pain. Due to intellectual property considerations, BDSI has not revealed the active ingredient in BEMA LA.

Clinical experience suggests that BEMA represents a nearly ideal delivery vehicle for analgesics that treat BTP.

MUCOSAL VERSUS TRANSDERMAL DELIVERY

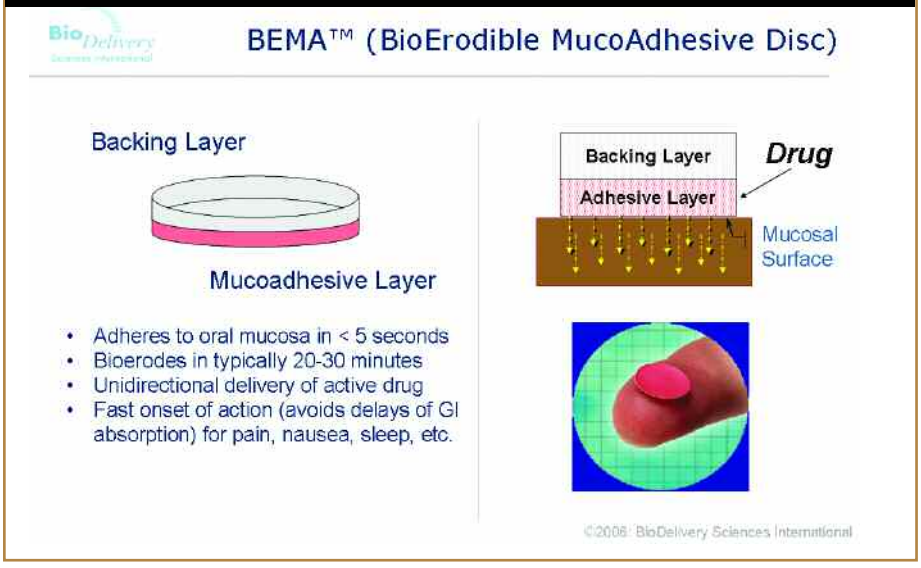
Mucosal delivery offers several key advantages over transdermal delivery. Lipophilic drugs like fentanyl are delivered rapidly and completely due to the high blood flow and the thin epithelial layer of the buccal mucosa. Topical irritation appears to be less of an issue with transmucosal delivery than with transdermal delivery. Because the blood vessels in the cheek tissue empty into the internal jugular vein, they sidestep hepatic first-pass metabolism. Similarly, transmucosal delivery avoids metabolism in the digestive tract and associated gastrointestinal side effects. Together, these advantages translate to safe, tolerable, rapid uptake of medication into the systemic circulation.

PHARMACOKINETICS

BEMA Fentanyl produces therapeutic plasma fentanyl concentrations in both a rapid and efficient manner. BEMA Fentanyl's well-defined physical dimensions and properties ensure optimal, predictable dosing and pharmacokinetics for treating BTP. With the BEMA formulation, the dose of fentanyl delivered to the patient is directly proportional to the size of the BEMA disc.

The ability to control dosing precisely through the formulation, and without patient effort, is of great benefit in treating BTP because in many cases, the condition incapacitates patients or makes them extremely uncomfortable. Patients or caregivers need only position the disc on the inner cheek. Tablets and lozenges require patients to maintain the dose

FIGURE 2



actively at the delivery site. This may seem trivial to healthy individuals, but patients in extreme pain often have difficulty keeping the dose in place.

Fentanyl doses beyond that contained in an individual disc (1,200 micrograms) may be administered through application of multiple BEMA discs. Because the dose is directly related to the surface area of the disc, clinicians can feel confident that plasma concentrations will increase in a linear manner if more than a single disc is used. BEMA Fentanyl has demonstrated linear pharmacokinetics at fentanyl doses up to 1,800 micrograms.

BEMA's occlusive barrier ensures that drug absorption is limited to oral mucosa and not the tongue or throat, where the unpleasant taste of the active fentanyl ingredient can affect compliance.

ABUSE POTENTIAL

No discussion of analgesia agents is complete without mentioning the potential for abuse. Like all high-strength painkillers, BEMA Fentanyl certainly has the potential to be diverted to individuals bent on abusing the drug. However, the BEMA delivery vehicle is perhaps the most tamper- and abuse-resistant formulation available. The active ingredient, fentanyl, is intimately dissolved in a polymer matrix that forms the BEMA disc. Unlike capsules or tablets, the BEMA matrix cannot simply be crushed and subsequently snorted or injected.

SUMMARY

Drug, delivery system, and patient/caregiver satisfaction are the keys to succeeding in the lucrative but competitive pain management marketplace. With its long record of safety and efficacy, fentanyl is one of a very small number of agents suitable for treating BTP. The BEMA delivery system provides an ideal mechanism for fentanyl delivery due to ease of use and predictable, linear pharmacokinetics. With the right drug and the right delivery vehicle, there is no longer any excuse for suboptimal treatment of serious pain.

BIOGRAPHY

Dr. Andrew L. Finn has been Executive Vice President of Clinical Development & Regulatory Affairs since September 2004, following the acquisition of Arius Pharmaceuticals, of which he is a Co-Founder. Prior to Arius, he was, from 2000 to 2003, Executive Vice President of Product Development at POZEN Inc. with responsibilities for formulation development, non-clinical development, clinical research and regulatory affairs. From 1996 to 1999, Dr. Finn was Co-founder and CEO of enVision Sciences, a regulatory and clinical service company. From 1991 to 1996, he was Vice President of US Clinical Research for Solvay Pharmaceuticals,Prior to this, he spent 10 years in positions of increasing responsibility at Glaxo Inc., where he oversaw a number of NDA submissions, including Zofran for chemotherapy-induced nausea and vomiting. Dr. Finn earned his BS in Pharmacy from the University of North Carolina and his Doctorate from the University of Michigan.

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EXTERNAL DELIVERY

The Yes Person Filter Factor, Part I

By: John A. Bermingham

One of the more dangerous situations that people face as they move higher in their organizations is the potential of being distanced from company problems. It's not their fault if it happens, it's inevitable. The higher a person moves in his or her organization, the less hands-on he or she can be. It's just a fact of life. A person's responsibility and what they need to focus on changes with their new job title. Let's examine why this happens. I call it the Yes Person Filter Factor.

The higher a person goes in an organization the more levels will exist between that person and the first level of employees in an organization. Say there are five levels of employees in an organization, and you are at the fourth or fifth level. That means that three or four levels of people exist between you and the first level of employees.

Now what happens when something bad occurs, and the situation is surfaced by a first-level employee. Well, that person will usually alerts their boss and so on up the chain of command until it gets to you. If you have a "yes person" in your chain of command, then you can be assured that the filter factor will go into action.

The conversation will go something like this with the yes person speaking here. "We have to let Joan (the boss) know about this problem right away. But let's soften the blow a bit so that she doesn't explode over this. Let's just tell her ……." So Joan receives filtered information from the yes person and ultimately makes the wrong decision.

Keep in mind that the yes person can be at any level, even the first level. But once the filter factor kicks in, you are in trouble. So I always get a bit paranoid when I continually hear good to fair news from a person but never bad news. Do you have a situation like this? More on the dreaded filter factor.

Some of the weaker senior level people also cause their own problems by surrounding themselves with yes people. Mega filter factor! These are senior managers who always want to hear their subordinates tell them that they are always right and want the bad news filtered out. These managers are certain that their ideas are working because the people around them tell them so, even when things are actually going south. I don't know whether this is caused by incompetence, insecurity, the dread of hearing bad news, etc, but it exists in every company.

Anyone can see it happening and pick out the Yes Person Filter Factors or those senior people who surround themselves with yes people, but what can you do about it? The answer to this question will appear in part two of this column as I let you all take some time to ponder what you would do. ◆

BIOGRAPHY

John A. Bermingham joined Ampad as President and CEO in August 2003 when Ampad was acquired by group of investors composed of an affiliate of Crescent Capital Investments, himself, and another private investor. He also serves as Chairman of the company's Board of Directors. Previously at the helm of numerous industry-leading companies, Mr. Bermingham brings more than 20 years' experience in guiding enterprises to new levels of performance. Most recently prior to joining Ampad, Mr. Bermingham held the positions of Chairman, President, and CEO of Centis, Inc., a diverse multinational manufacturer and marketer of office, storage, and human resources products. Prior to joining Centis, Mr. Bermingham successfully leveraged the potentials of two start-up companies, raising capital, forging key relationships, and establishing the structure and direction that would pave the way for future growth and achievement. Among his many career highlights in the role of President and CEO for companies serving the office products industry, Mr. Bermingham successfully reorganized Smith Corona Corporation, restoring the company's stability, profitability, and reputation. At Rolodex Corporation, he refocused operations and a strategic vision for a dramatic turnaround in corporate culture, and phenomenal increases in both revenue growth and cashflow. Mr. Bermingham's expertise in leveraging technology and optimizing resources for the business products/services markets 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. Earning a BA in Business Administration from Saint Leo University in Florida, Mr. Bermingham has also completed the Harvard University Graduate School of Business Advanced Management Program.

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