Drug Delivery® Technology

January 2006 Vol 6 No 1

Overcoming Solubilization Challenges

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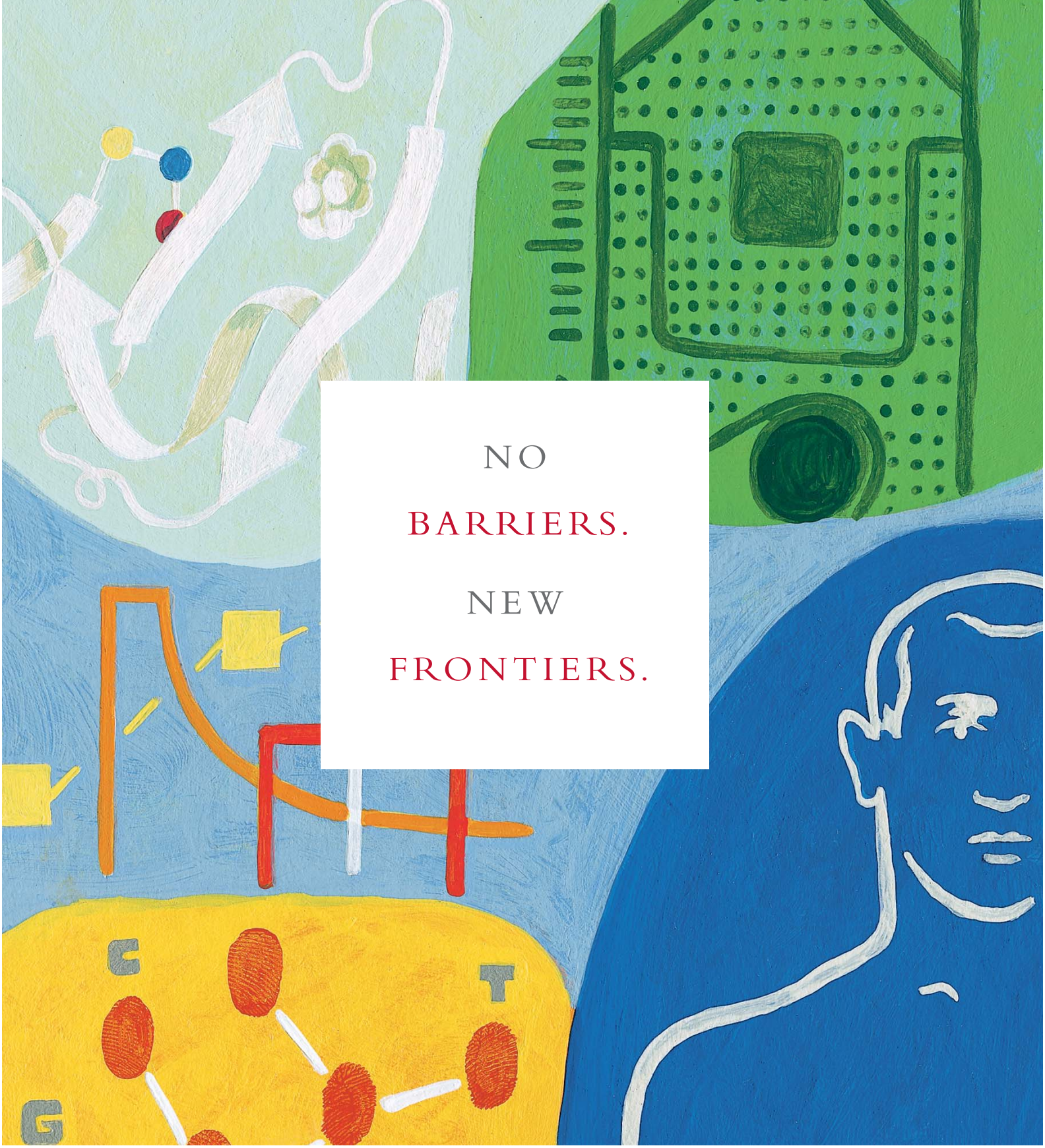

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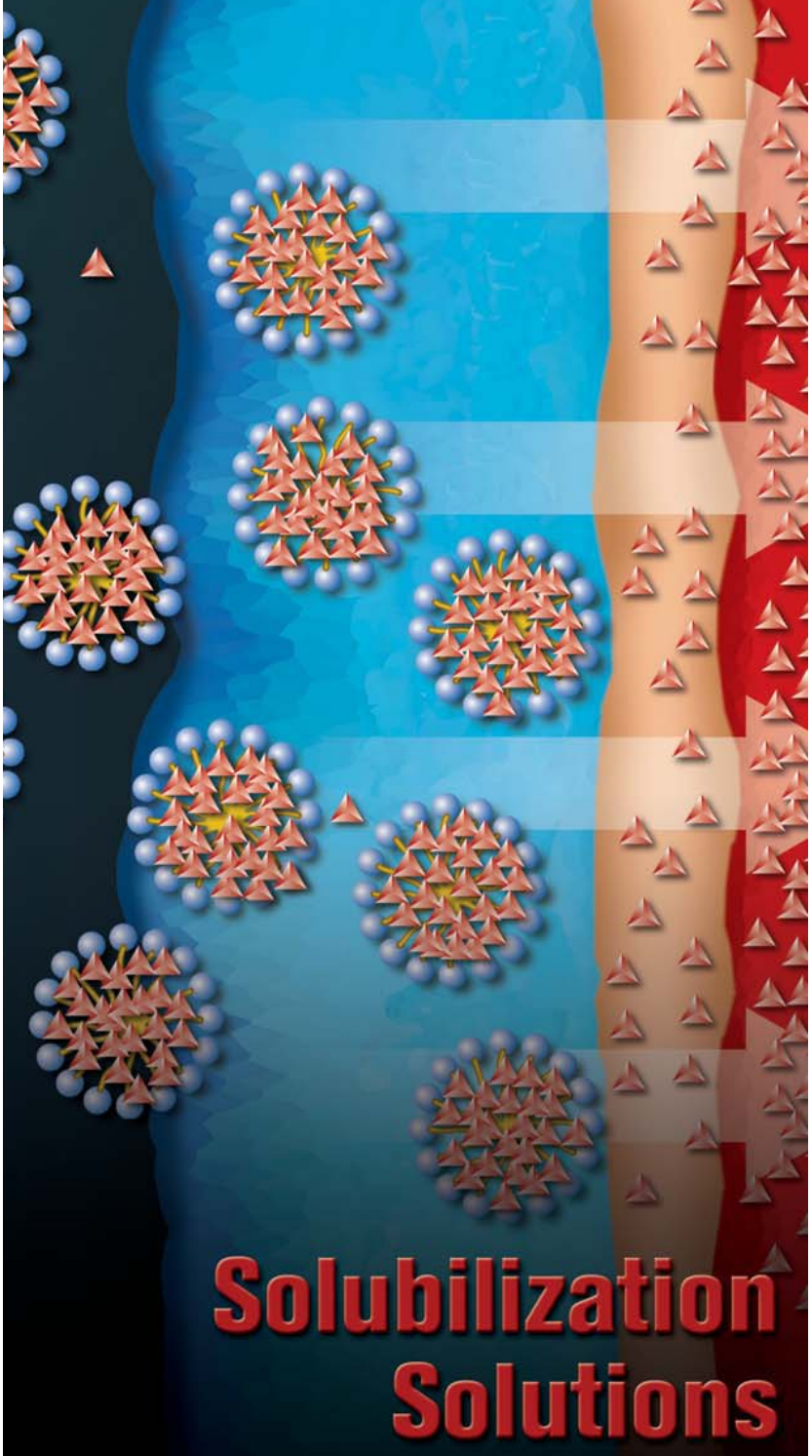

Solubilization Solutions

"The potential advantages of the Lip'ral systems include fastest absorption, lowest effective dose, least variable absorption, and flexibility in administration due to the lack of dependence on physiological factors, including presence or absence of food."

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Unparalleled taste Flexible dose Versatile release Robust tablet

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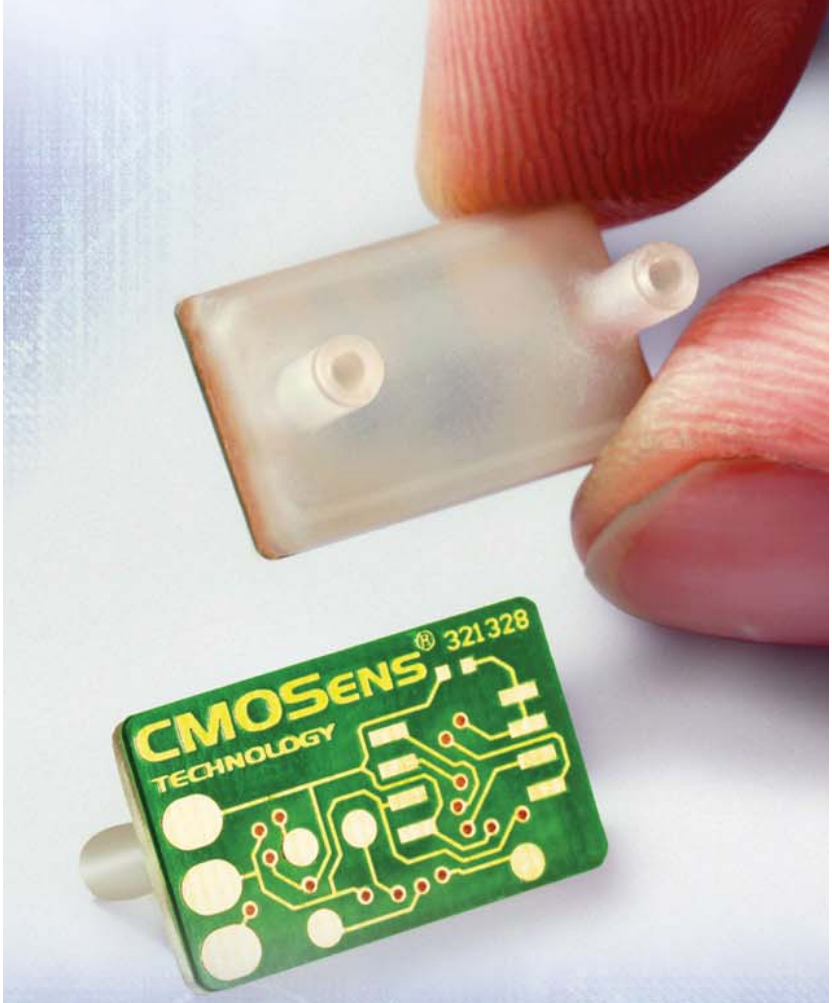

Measurement Technology

"The scope of the technical options for increasing the safety and accuracy of drug delivery systems and adding supplementary electronic monitoring and control features has been enlarged significantly. The key are fully calibrated single-chip solutions."

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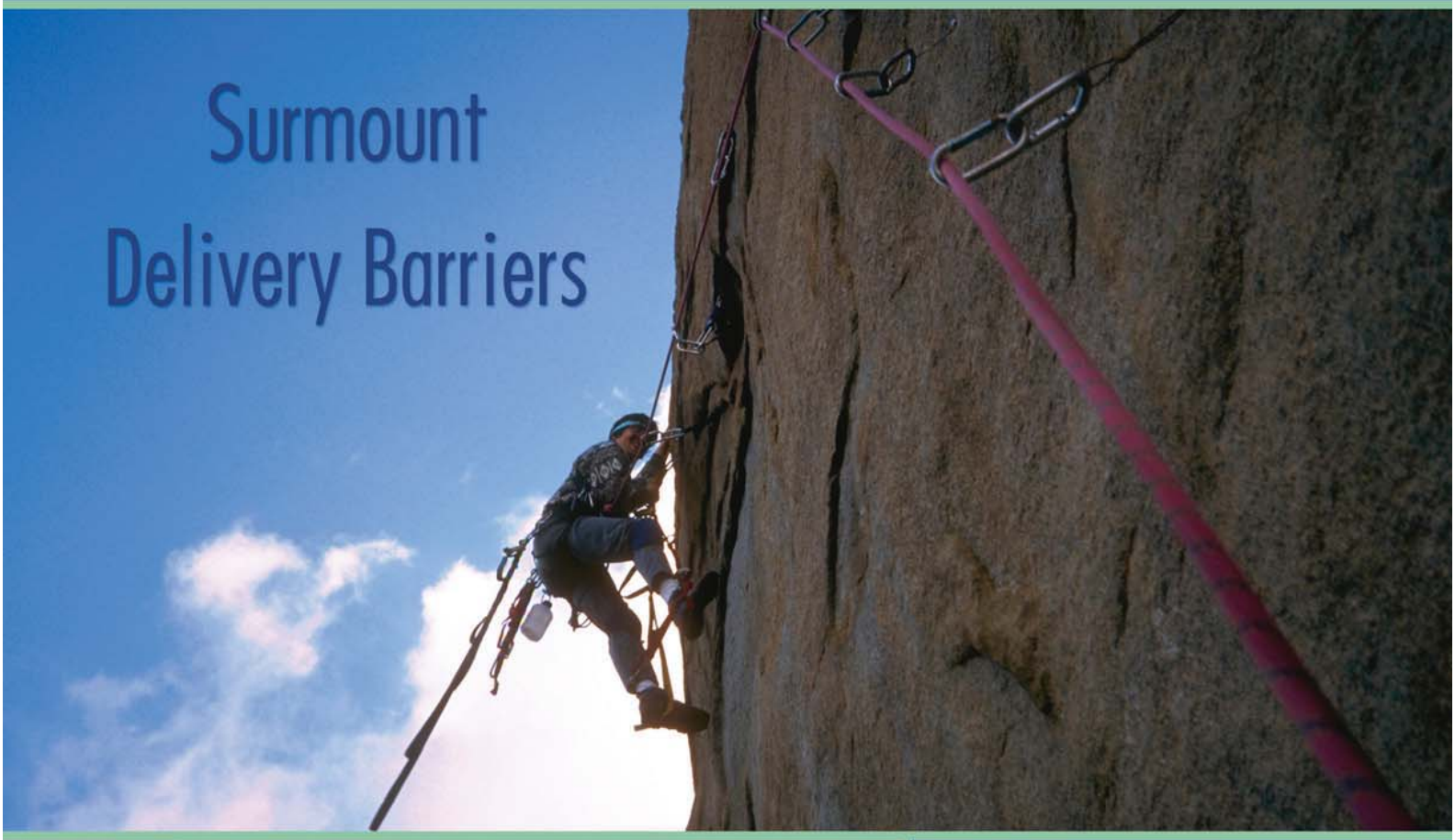
Surmount Delivery Barriers



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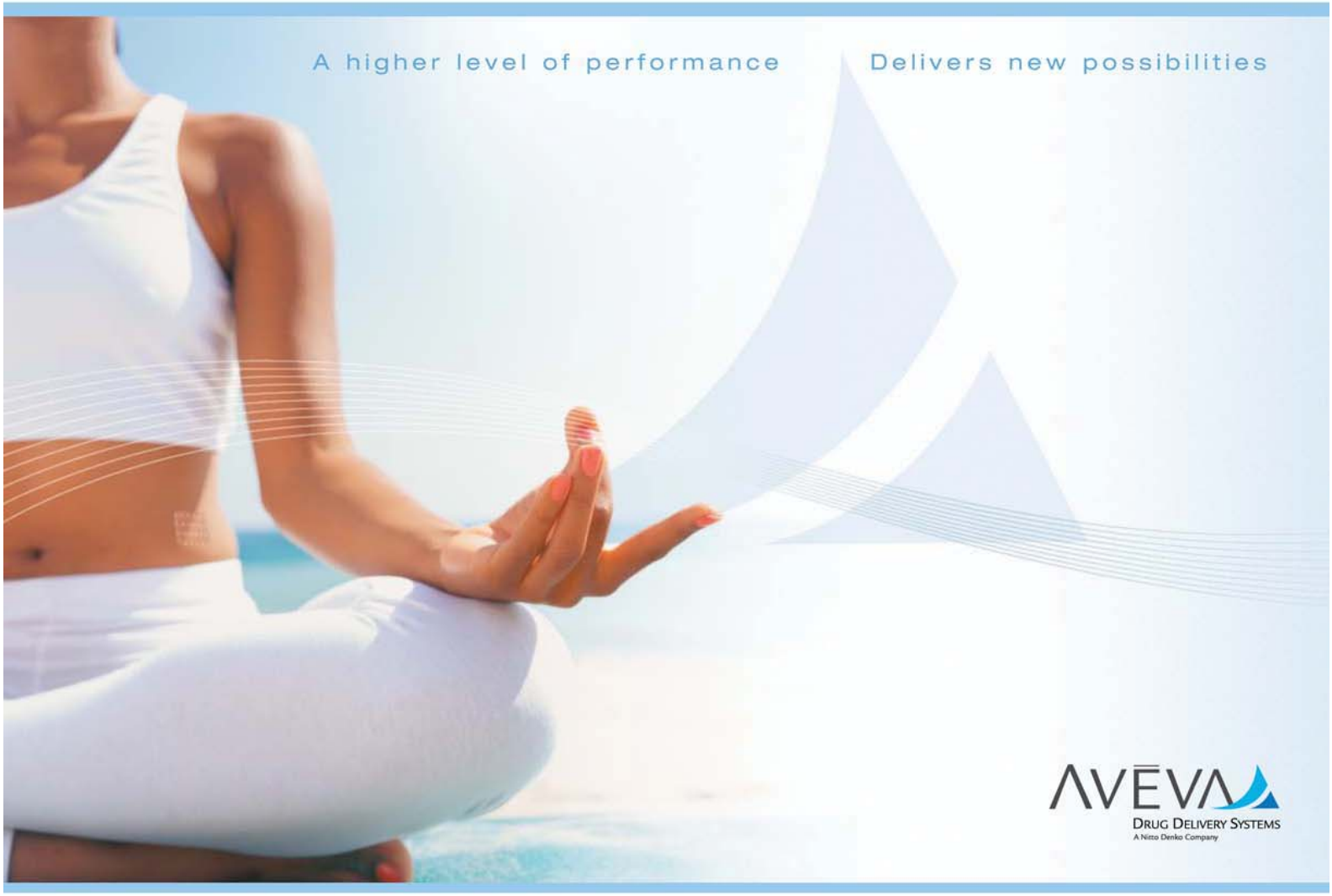

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MARKET NEWS and TRENDS

GlaxoSmithKline & Vertex Pharmaceuticals Announce Collaboration to Develop & Commercialize Novel Pain Compound

GlaxoSmithKline and ***Vertex Pharmaceuticals Incorporated*** recently announced they have entered into a new agreement to develop and commercialize VX-409, Vertex's novel, subtype selective sodium channel modulator for the treatment of pain. VX-409 is the first of a new class of agents targeting specific pain signals in nerve cells. Under the terms of the agreement, GSK will have the exclusive right and license to develop and commercialize VX-409 and back-up compounds worldwide. Vertex will receive a $20 million upfront payment and could receive up to an additional $385 million in development and sales threshold milestone payments based on the development of VX-409 and back-up compounds in major pharmaceutical markets across a range of indications. GSK will also pay Vertex royalties on annual net sales.

"This is another example of GSK's commitment to invest in external opportunities that complement our existing disease area expertise and maximize our development of innovative and best-in-class medicines to address unmet medical needs in key clinical areas," said Dr. Jackie Hunter, Senior Vice President, Neurology and GI Centre of Excellence for Drug Discovery, GSK.

"GlaxoSmithKline is a leader in the development of new treatments for chronic and acute pain, and we are pleased to join with GSK to develop and commercialize VX-409 for the treatment of a variety of pain indications," said Joshua Boger, PhD, Chairman, President and CEO of Vertex. "VX-409 may have the potential to change the future management of pain, based on the clinical confirmation of the compound's profile."

VX-409 is a leading agent in a new class of investigational therapies targeting pain treatment through selective modulation of sodium channels in nerve cells. Specific sodium channels are involved in transmitting sensory input, including the transmission of pain signals to the central nervous system, making them attractive targets for new pain treatments. As an oral, subtype selective sodium channel modulator, VX-409 has been shown to be orally bioavailable, highly active, and has exhibited a good safety profile in nonclinical models of both neuropathic and inflammatory pain. VX-409 was discovered through Vertex's San Diego-based ion channel research program using the capabilities and proprietary technologies that are unique to that site. Phase I clinical development of VX-409 is expected to be initiated early in 2007.

In the United States, an estimated 14 million people are affected by inflammatory pain, and 3 million by neuropathic pain. Worldwide prescription drug sales for the treatment and management of pain were more than $20 billion in 2004, and are projected to grow at an estimated 10% annually through 2008. Both neuropathic and inflammatory pain are areas of major unmet medical need, and a new treatment targeting these areas could represent a significant product opportunity.

Vertex Pharmaceuticals Incorporated is a global biotechnology company committed to the discovery and development of breakthrough small molecule drugs for serious diseases. The company's strategy is to commercialize its products both independently and in collaboration with major pharmaceutical companies. Vertex's product pipeline is principally focused on viral diseases, inflammation, autoimmune diseases, and cancer.

V-Kardia Inc. Announces Successful Preclinical Trials for Targeted Drug Delivery

V-Kardia, Inc., recently announced that academic investigator, David Kaye, MD, PhD, of the Baker Heart Research Institute, presented preclinical results on the successful use of the company's new targeted delivery system (V-Focus™) for administering therapeutic genes directly to the heart. The results demonstrated the ability of the system to selectively deliver therapeutic levels of a gene to the heart, with minimal leakage into the systemic circulation, significantly restoring heart function in a large animal model of heart failure. These data were presented at the recent American Heart Association Scientific Sessions in Dallas, Texas.

Heart failure is a leading cause of hospitalization, disability, and death, with over 5 million people in the United States suffering from the disease. Despite significant advances in pharmacotherapy, heart failure remains a progressive disorder with 5-year survival of less than 50%. Recently, many of the molecular and cellular mechanisms causing the impairment of heart function have been determined. Recent studies using a range of gene therapy approaches targeting these mechanisms have raised hopes for the treatment of heart failure. However, until now, there has not been a reliable means of delivering a therapeutic gene directly to the heart.

Professor David Kaye, working with colleagues from Massachusetts General Hospital and Harvard University, presented data which described the ability of the V-Focus System to allow targeted delivery of genes, molecules, and cells to the heart and potentially other organs and tissues. In the cardiac application, Professor Kaye described how the V-Focus system was used to isolate the coronary circulation from the general circulation and effectively deliver gene therapy to a large animal model of heart failure. The system was introduced percutaneously and delivered the agent safely and efficiently. High, uniform levels of the test agent were found within the heart tissue while little to no agent was found in the lungs, liver, or kidneys. The results confirmed that this delivery system can be used for the delivery of gene therapy to the severely failing heart, significantly restoring heart function.

V-Kardia, Inc., is a privately held company based in St. Paul, Minnesota. The company is focused on the development of percutaneous delivery systems for targeted agent delivery to an organ or body region. The initial product, the V-Focus System, is designed to deliver high, uniform level of agents to the heart while minimizing delivery to the other organs or areas of the body. The company is actively seeking other gene- based and cell therapies for use with the V-Focus System. V-Kardia was founded in conjunction with the Baker Heart Research Institute of Melbourne, Australia.

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Kurve Technology Develops Intelligent Nasal Drug Delivery Device

Kurve Technology, Inc. is launching the first nasal drug delivery device that incorporates drug identification and lock-out technologies, data transfer, and an electronic display - features that not only improve patient compliance but could prove to be important in curbing the multibillion dollar counterfeit drug market.

The latest in Kurve Technology's drug delivery device line, ViaNase ID™ uses the company's proprietary technology to control which drugs are used in the device. The attempted use of an unapproved drug renders the device inoperable. ViaNase ID also records such information as drug name, product code, and expiration date. This data can be saved to a data storage card or downloaded to a PC or PDA - useful for physicians, pharmacies, and patients.

ViaNase ID also simplifies the administration of nasally delivered drugs. On the electronic display, patients can see the number of doses delivered, number of doses left in the prescription, as well as receive alarm reminders when it's time to administer the drug.

As with ViaNase, the company's first nasal drug delivery device, Kurve will license ViaNase ID to select pharmaceutical companies on a globally exclusive arrangement by therapeutic class.

Counterfeit drugs are fake medicines (sugar pills), poorly manufactured substitutes, or generic medicines that are deliberately mislabeled so that the consumer gets the impression that they are authentic, approved products. A recent report released by the Center for Medicines in the Public Interest projects counterfeit drug sales to reach $75 billion by 2010.

In attempts to curb drug counterfeiting, the pharmaceutical industry with the support of the Federal Drug Administration is developing a "pedigree" system that will track prescription drugs from production sites to retail pharmacies. However, tracking ends at the pharmacy. ViaNase ID picks up where this system leaves off by validating the pedigree of the drug at the device level, a step that could significantly curtail the use of counterfeit drugs and the misuse of correctly prescribed drugs.

"Both the FDA and the pharmaceutical industry have expressed great interest in curtailing the counterfeit drug market," said Marc Giroux, CEO of Kurve Technology. "As a truly intelligent nasal delivery device, ViaNase ID offers pharmaceutical companies one of the first methods at the patient level to confirm the drug is authentic."

Kurve Technology, Inc. offers pharmaceutical companies versatile nasal delivery systems for local and systemic medical therapies. Kurve's Controlled Particle Dispersion (CPD)™ technology intranasally delivers compounds with far greater efficacy and efficiency than traditional methods. The ViaNase product line of intelligent atomizers incorporates CPD to deliver a wide range of compounds, aiding the more than 200 million patients who suffer from such medical conditions as allergic rhinitis, chronic rhinosinusitis, sexual dysfunction, migraine headache, obesity, and CNS disease.

Nastech Presents New Methods for Peptide & Protein Drug Delivery

Nastech Pharmaceutical Company, Inc., a leader in developing therapeutics using advanced molecular biology-based drug delivery technologies, recently announced the presentation of data from the company's transmucosal peptide and protein drug delivery program at The American Society for Cell Biology in San Francisco. The purpose of this program is to further advance the development of non-injectable methods for administering large molecule therapeutics that would otherwise require patient injections.

The presentation, titled Peptide Drug Permeation Enhancement by Select Classes of Lipids, includes data that demonstrates the potential for four new classes of lipids to enhance transmucosal delivery of peptides and proteins. Among seven groups of lipids tested (sterols, sphingolipids, ceramides, glycosylated sphingosines, alkylglucosides, oxidized lipids, and ether lipids), the latter four were identified as tight junction modulators. Alkylglucosides, however, showed very high cytotoxicity and low cell viability at concentrations (0.2% to 0.4%) reported to enhance transmucosal absorption when compared to the other three lipid classes and a recently identified tight junction modulating peptide. Lipids that rapidly and reversibly alter tight junction permeability, an important factor in regulating paracellular drug transport, were identified utilizing the company's proprietary high-throughput tissue screening model. These lipids were shown to significantly enhance peptide permeation through epithelial tissue.

Nastech believes that the finding that oxidized lipids activate tight junctions may help solve mechanistic questions about the origin of atherosclerosis. It has been shown that oxidized lipids in the vascular system initiate a cascade of responses culminating in an inflammatory response that leads to the development of atherosclerosis.

The company also believes its original research demonstrates an interaction between oxidized lipids and tight junctions of cells, raising the prospect for a new therapeutic approach to cardiovascular disease.

Nastech has previously demonstrated the ability to significantly enhance transmucosal drug delivery of large molecule therapeutics using small molecules and peptides as delivery agents. The lipids identified in this study are believed to represent a new class of molecules that have the potential to improve the delivery of these types of therapeutics.

Halozyme Therapeutics & Baxter Healthcare Announce FDA Approval of Hylenex

Halozyme Therapeutics, Inc., a biopharmaceutical company focused on the development and commercialization of recombinant human enzymes, and Baxter Healthcare Corporation recently announced the US FDA has approved Halozyme's Hylenex recombinant (hyaluronidase human injection) for use as an adjuvant agent to increase the absorption and dispersion of other injected drugs. Baxter will market and sell Hylenex, a proprietary recombinant human hyaluronidase, in the US.

"We are thrilled that the FDA has approved our first NDA filing," said Jonathan Lim, MD, Halozyme's Chairman and CEO. "This is a landmark achievement for Halozyme. We believe Hylenex will help enhance the practice of medicine by offering healthcare providers and their patients a human recombinant product as an adjuvant to increase the absorption of other injected drugs."

"We look forward to using our expertise and strong channels to successfully launch Hylenex, allowing patients in many clinical settings to benefit from the product manufactured with this promising technology," said Daniel Tasse, General Manager of Baxter's Anesthesia, Critical Care, and Oncology business. "We will continue to work with Halozyme to help clinicians fully realize the drug delivery and administration benefits this product offers."

Results from a clinical trial conducted to support the Hylenex NDA demonstrated no allergic reactions to Hylenex and significantly reduced injection site discomfort. The double-blinded clinical study compared Hylenex to a saline control in 100 human volunteers. These volunteers were injected intradermally with Hylenex in one forearm and saline control in the other forearm, and evaluated for allergic responses and injection site side effects. The data showed injection site discomfort (eg, stinging, burning, other discomfort) of 28% in the saline arm and 3% in the Hylenex arm.

Hylenex recombinant (hyaluronidase human injection) is indicated for use as an adjuvant agent to increase the absorption and dispersion of other injected drugs, for hypodermoclysis, and as an adjunct in subcutaneous urography for improving resorption of radiopaque agents. Hylenex recombinant is contraindicated in patients with hypersensitivity to hyaluronidase enzyme or any other ingredients in the formulation. The contraindications and warnings regarding the use of Hylenex should be recognized and adhered to prior to prescription or administration.

Baxter Healthcare Corporation is the principal US operating subsidiary of Baxter International Inc. Baxter International Inc., through its subsidiaries, assists healthcare professionals and their patients with the treatment of complex medical conditions, including cancer, hemophilia, immune disorders, kidney disease, and trauma. The company applies its expertise in medical devices, pharmaceuticals, and biotechnology to make a meaningful difference in patients' lives.

Halozyme is a biopharmaceutical company dedicated to developing and commercializing recombinant human enzymes for the infertility, ophthalmology, and oncology communities. The company's portfolio of products under development is based on intellectual property covering the family of human enzymes known as hyaluronidases. Halozyme's recombinant human enzymes may replace current animal slaughterhouse-derived enzymes that carry potential risks of animal pathogen transmission and immunogenicity. The versatility of the first enzyme, rHuPH20, enables Halozyme to develop the product as a medical device, drug enhancement agent, and therapeutic biologic.

Inyx Selected to Develop HFA Combination Metered Dose Inhaler

Inyx, Inc., recently announced that its wholly owned subsidiary, Inyx Pharma Limited, has been selected by a European pharmaceutical company to develop a combination between a corticosteroid and a beta-2-agonist in a single metered dose inhaler (MDI) utilizing a non-ozone-depleting hydrofluoroalkane (HFA) propellant.

Corticosteroids are the most effective and widely used anti-inflammatory drugs for the treatment of bronchial asthma and other chronic obstructive pulmonary diseases (COPD), such as bronchitis and emphysema. They are often taken with short-acting or long-acting bronchodilators (beta-2-agonists) that are the primary rescue medicine used to treat asthma and other COPD attacks. Today, more and more physicians are prescribing for chronic asthma sufferers combination therapy as a regular drug regimen.

"We are very pleased that Inyx has been selected for this client's important HFA program," said Jack Kachkar, MD, Chairman and CEO of Inyx, Inc. "This represents Inyx's first combination drug-MDI development work for a client."

Inyx is initially developing test batches in different dosages for the client. This will be followed by stability testing, which is targeted for mid-2006. Commercial production is aimed for 2007.

"Being able to deliver corticosteroid and beta-2-agonist in a single inhaler will not only mean added convenience but also should provide cost savings to consumers because it eliminates the need for buying and carrying two separate inhalers, which should make this a strong competitive product. Moreover, by using an HFA propellant, our client will be able to market this combination therapy throughout Europe," added Dr. Kachkar. The European Union has banned the use of the ozone-depleting CFC (chlorofluorocarbon) propellant in pharmaceutical products, and the US is starting to implement this ban.

Inyx, Inc., is a specialty pharmaceutical company with niche drug delivery technologies and products for the treatment of respiratory, allergy, dermatological, topical, and cardiovascular conditions. Inyx focuses its expertise on both prescription and over-the-counter pharmaceutical products, and provides specialty pharmaceutical development and production consulting services to the international healthcare market. In addition, Inyx is developing its own proprietary products to be marketed by selected clients and strategic partners, which include some of the largest pharmaceutical companies.

BDSI Announces Supply Agreement With Aveva Relating to BEMA™ Fentanyl

BioDelivery Sciences International, Inc., a specialty pharmaceutical company, recently announced it has entered into a supply agreement with Aveva Drug Delivery Systems, Inc. (Aveva) under which Aveva will prepare clinical supplies for BDSI's Phase III trials and provide commercial manufacturing for BEMA™ Fentanyl. BDSI's BEMA Fentanyl is an oral adhesive disc formulation of the narcotic fentanyl. BDSI has been and expects to continue its production ramp-up of the clinical trial materials for Phase III BEMA Fentanyl trials during the fourth quarter of 2005. BDSI plans on completing its

Phase III program during the second half of 2006 for the treatment of "breakthrough" cancer pain (ie, episodes of severe pain which "breakthrough" the medication used to control the persistent pain).

In related BEMA Fentanyl news, BDSI recently reported positive results in a pharmacokinetic study comparing BEMA Fentanyl and Actiq®, a lozenge formulation of fentanyl, which is the current market leader in fast-dissolving fentanyl products in treating breakthrough cancer pain. In this trial, BEMA Fentanyl enabled greater bioavailability (absorption), higher maximum plasma concentrations (Cmax), and faster concentrations of fentanyl in the plasma (t-first and t-max) compared to Actiq.

Actiq, made by Cephalon, Inc., is considered the market leader in breakthrough cancer pain treatment with projected 2005 sales, based on Cephalon's public statements, between $410 and $420 million.

"We are very pleased to be able to work with Aveva toward the production of the BEMA Fentanyl product," said Dr. Mark Sirgo, President and CEO of BDSI. "The entry into this agreement represents the fulfillment of a key component of our BEMA Fentanyl strategy. With this agreement in place, we are well positioned for manufacturing of the Phase III program supplies and, if FDA approval is obtained, the ultimate commercial launch of BEMA Fentanyl."

"In our recent pharmacokinetic study, we experienced excellent results with large production batches of BEMA Fentanyl manufactured at Aveva," added Dr. Andrew Finn, BDSI's Executive Vice President of Clinical and Regulatory Affairs. "We believe Aveva's capabilities will, at the appropriate time, allow us to move into commercial scale very quickly."

Wallace K. Reams, President and Chief Operating Officer of Aveva, stated "We are pleased to bring Aveva's depth of experience in transdermal and transmucosal drug delivery systems to the BEMA Fentanyl program. Our arrangement with BDSI further demonstrates our commitment to add value to our partners."

Under the terms of the supply agreement, Aveva, of Miramar, Florida, will have the exclusive right to manufacture and supply the BEMA Fentanyl discs to BDSI, which will, either alone or in partnerships with other third parties, market, sell, and distribute the product within North America.

Aveva Drug Delivery Systems, Inc., is a Nitto Denko company, which is one of the world's largest manufacturers of and a pioneer in transdermal drug delivery systems. Nitto Denko has a 20-year history of providing pharmaceutical partners with fully integrated, controlled-release transdermal products that fulfill unmet market needs or are high-quality, low-cost brand equivalents. Leveraging this experience, Aveva offers a full range of research, development, and manufacturing capabilities using a number of sophisticated technologies to produce proprietary and generic transdermal drug delivery systems that fortify research and development pipelines and maximize the life cycles of products.

BioDelivery Sciences International, Inc., is a specialty biopharmaceutical company that is exploiting its licensed and patented drug delivery technologies to develop and commercialize, either on its own or in partnerships with third parties, clinically significant new formulations of proven therapeutics targeted at "acute" treatment opportunities, such as pain, anxiety, nausea, and vomiting, and infections. The company's drug delivery technologies include: (i) the patented Bioral® nanocochleate technology, designed for a potentially broad base of applications, and (ii) the patented BEMA (transmucosal or mouth) drug delivery technology.

Emisphere Announces Positive Results From Clinical Study Conducted By Independent Investigators Using Oral Salmon Calcitonin in Osteoarthritis Patients

Emisphere Technologies, Inc., recently announced that positive clinical data generated by Drs. Daniel Manicourt and Jean-Pierre Devogelaer from the Department of Rheumatology at the University Hospital St-Luc, Universite Catholique de Louvain, Brussels, Belgium evaluating oral salmon calcitonin (CT) supplied by Novartis Pharma AG using Emisphere's eligen® technology in treating osteoarthritis (OA) were presented at the 10th World Congress of the Osteoarthritis Research Society International (OARSI) in Boston. Results of this study strongly suggest that Oral CT (enabled by Emisphere's proprietary eligen technology licensed to Novartis for the use with calcitonin) exhibits not only clinical efficacy but also reduces markedly the levels of several biochemical markers of joint metabolism, which all have been shown to have a pejorative prognostic value of the OA disease process in longitudinal studies, including large cohorts of patients.

The randomized, double-blind, placebo-controlled, parallel study was conducted for 3 months in OA patients to assess the efficacy of this novel form of CT in patients suffering from knee OA. Patients received daily either a placebo (n=16), 0.5 mg of oral CT (n=17), or 1 mg of oral CT (n=18).

Clinical efficacy on pain, function, and stiffness were evaluated by Lequesne's algofunctional indices (LI). In the placebo group, there was no significant change in the mean +/- SD value of LI. In the two CT groups, the mean value of LI was similar at day 0 (15.4 +/- 2.6), and was significantly decreased at day 84 (10.6 +/- 3.8 in the 0.5 mg group, and 9.6 +/- 3.2 in the 1 mg group).

Biochemical parameters of joint metabolism, as assessed by enzyme immunoassays, included urinary levels of type I and type II collagen C telopeptide (CTX-I and CTX-II, respectively) as well as serum levels of type II collagen neoepitope C2C, matrix metalloproteinase (MMP)-3, collagenase-3 (MMP-13), tissue inhibitors 1 and 2 MMPs (TIMP-1 and TIMP-2) and hyaluronan (HA). Statistical analysis included analysis of variance followed by Tukey test whenever needed.

When compared to values at study entry, levels of biochemical parameters had changed significantly in all groups at day 84 ($p < 0.05$ to 0.01). In the placebo group, there was a significant increase in the mean urinary levels of both CTX-1 (15%), CTX-II (9%) and in the mean serum levels of C2C (29%), MMP-13 (153%), MMP-3 (49%), and HA (25%). In contrast, in the 1 mg CT group, there was a significant decrease in the mean urinary levels of both CTX-1 (10%), CTX-II (21%) as well as in the mean serum levels of C2C (25%), MMP-13 (40%), MMP-3 (18%), and HA (28%). Results obtained in the 0.5 mg CT group were intermediate between the other groups and are not reported. No change in the mean serum levels of TIMP-1 and TIMP-2 was observed in the three groups.

The number of withdrawals was 2 in the placebo group (lack of efficacy), 4 in the 0.5 mg CT group (1 for lack of efficacy and 3 for nausea and headache), and 4 in the 1 mg CT group (2 for protocol violation and 2 for nausea and headache).

"This pilot study, conducted by the University Hospital St-Luc, Universite Catholique de Louvain, Brussels Belgium demonstrated the ability of the 1-mg dose of our unique oral salmon calcitonin product to not only show clinical efficacy in the study, but also demonstrated a decrease in biochemical markers that have been correlated with continued joint degradation. Over the course of the 84-day study, the placebo patients had no statistically significant change in clinical scores, while they had statistically significant increases in biochemical markers that have been correlated with continued joint degradation. We are encouraged by these results and look forward to Novartis commencing pivotal Phase III studies of Oral CT in early 2006," said Michael M. Goldberg, MD, Chairman and Chief Executive Officer of Emisphere Technologies. "The success of Oral CT in this Phase II study provides hope for the tens of millions of patients worldwide suffering with OA. There are currently no proven pharmaceutical products that can impact on the progression of this chronic disease. Nordic Bioscience presented two additional papers at the OARSI conference that further elucidate the mechanism by which oral calcitonin positively impacts on OA progression."

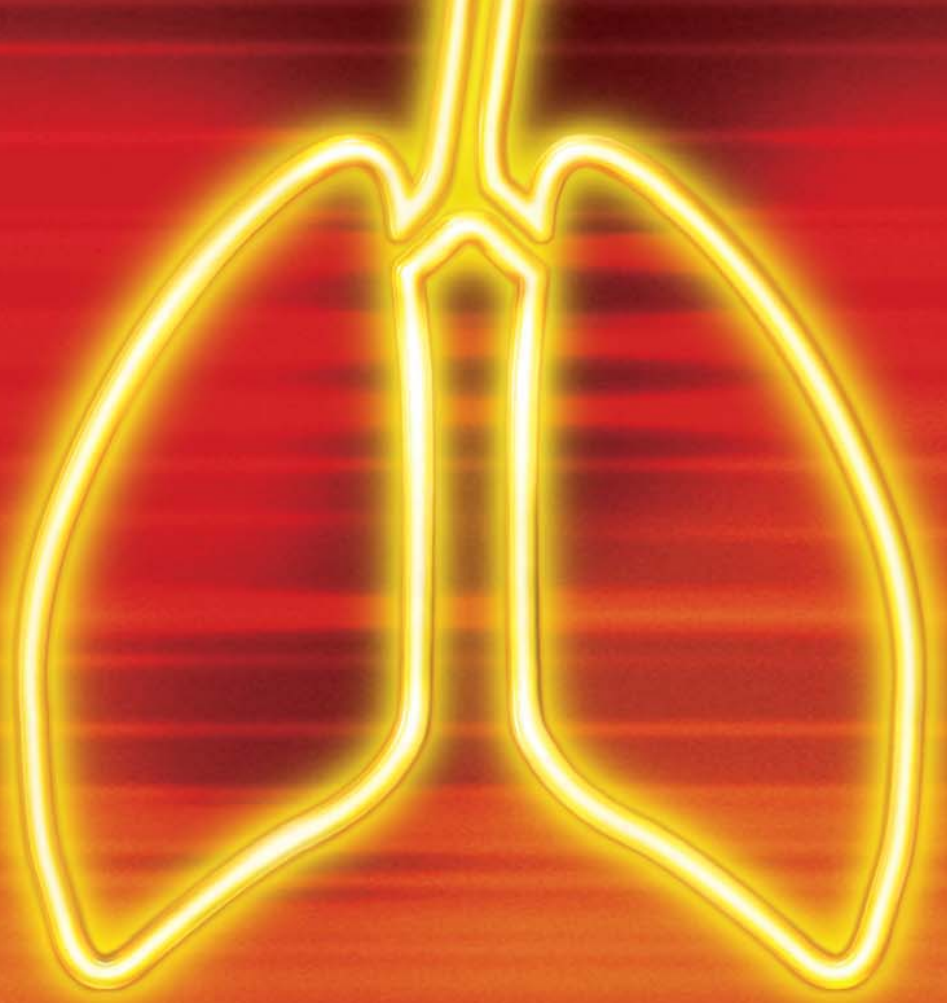
Merck Announces US Label Change for Singulair®: Clinical Study Shows Children Taking Drug Maintained Similar Growth Rates Compared to Placebo

Merck & Co., Inc., recently announced changes to the product label for Singulair (montelukast sodium), which includes new information from a 56-week clinical study that demonstrated children with asthma (6 to 8 years of age) taking Singulair 5-mg tablets once daily had similar growth rates as children taking placebo. In the same study, children taking the inhaled steroid beclomethasone dipropionate 168 mcg twice daily had slower growth rates than children on either Singulair or placebo.

"The new label language provides physicians and patients with important new information on Singulair that should prove helpful in furthering their understanding of the medicines used in the treatment of asthma," said Theodore F. Reiss, MD, Vice President, Clinical Research, Merck Research Laboratories.

Results from the 56-week, multicenter, double-blind, randomized active, and placebo controlled parallel group study of 360 patients with mild asthma showed that the differences in growth rates, expressed as least-squares (LS) mean [95% confidence interval (CI)] in centimeters (cm)/year, for Singulair minus placebo, beclomethasone minus placebo, and Singulair minus beclomethasone treatment groups were 0.03 (CI, -0.26, 0.31), -0.78 (CI, -1.06, -0.49); and 0.81 (CI, 0.53, 1.09), respectively. The primary comparison was the difference in growth rates between Singulair and placebo groups.

Growth rates, expressed as LS mean (95% CI) in cm/year, for the SINGULAIR, placebo, and beclomethasone treatment groups were 5.67 (CI, 5.46, 5.88), 5.64 (CI, 5.42, 5.86), and 4.86 (CI, 4.64, 5.08), respectively. Treatment groups included SINGULAIR 5 mg once daily, placebo, and beclomethasone dipropionate administered as 168 mcg twice daily with a spacer device.



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Carrington Granted European Patent for Drug Delivery Technology

Carrington Laboratories, Inc., recently announced that the European Patent Office has issued European Patent No. EP 1 086 141 B1, titled Aloe Pectins, relating to the company's proprietary GelSite® polymer technology. DelSite Biotechnologies, Inc., Carrington's wholly owned subsidiary, is developing and commercializing GelSite polymer as a controlled-release drug delivery technology for pharmaceutical and vaccine products.

The newly issued patent describes the basic composition and process of manufacturing high-molecular weight and low-molecular-weight pectins from Aloe vera. The claims of this patent are broadly applicable to any use of DelSite's Aloe pectins, including use in pharmaceutical compositions, including proteins, peptides, vaccine antigens, and other pharmacological substances.

"DelSite continues to build a strong intellectual property estate around our proprietary drug delivery technologies, and we are pleased to receive the first European patent for GelSite polymer," said Kenneth Yates, President of DelSite Biotechnologies. "GelSite polymer has unique functional properties, such as in situ gellation and the ability to stabilize many proteins that make it an attractive basis for novel drug delivery systems, including the GelVac™ nasal powder vaccine delivery system."

DelSite's most advanced delivery platform is the GelVac nasal powder vaccine delivery system based on GelSite polymer. GelVac is a simple and broad nasal powder vaccine delivery platform suitable for many different classes of vaccine antigens. In May 2005, DelSite announced results of a Phase I clinical trial involving 15 healthy volunteers that demonstrated that the GelSite polymer and the GelVac system was safe and well tolerated and that doses were consistently and reproducibly delivered to the nasal cavity. A Drug Master File (DMF) for use of GelSite polymer in mucosal applications was recently filed with the FDA. Currently, preclinical development is progressing for a GelVac nasal powder avian influenza (bird flu) vaccine.

GelSite polymer is a naturally sourced, high molecular weight anionic polysaccharide that exhibits distinct chemical and functional properties proprietary to the company. GelSite is water-based and is capable of *in situ* gelation, ie, changing either a solid or liquid formulation into a gel upon contact with body fluids leading to controlled-release of active biomolecules. GelSite is not an adjuvant and is a member of a family of plant polysaccharides classified by the FDA as Generally Regarded As Safe (GRAS). The polymer is currently manufactured to cGMP standards at Carrington's wholly owned subsidiary, Sabila Industrial, S.A., in Costa Rica.

The GelVac system is a nasal powder vaccine delivery platform based on GelSite polymer. Dry powder formulations delivered nasally provide several potential advantages, including better stability, room temperature storage, no need for preservatives, no need for needles, and mucoadhesive. Nasal immunization induces both systemic and mucosal immune responses. The GelVac delivery system increases antigen nasal residence time providing for prolonged contact with the mucosal surface, which may improve immune response for many different classes of antigens.

Carrington Laboratories, Inc., is an ISO 9001-certified, research-based, biopharmaceutical and consumer products company currently utilizing naturally occurring complex carbohydrates to manufacture and market products for mucositis, radiation dermatitis, wound and oral care, as well as to manufacture and market the nutraceutical raw material Manapol® and cosmetic raw material Hydrapol™. Carrington also manufactures and markets consumer products under the AloeCeuticals® brand and manufactures quality products for other companies.

Protein Polymer Technologies Announces Intention to Merge With Thuris Corporation

Protein Polymer Technologies, Inc., a biotechnology device company that is a pioneer in protein design and synthesis, recently announced it has signed a letter of intent to merge with Thuris Corporation, a privately held biopharmaceutical company focused on medical device solutions to aid in drug development and diagnosis of Central Nervous System (CNS) disorders, including Mild Cognitive Impairment and Alzheimer's Disease. Thuris is also developing pharmaceuticals for select CNS Orphan and niche indications ranging from ischemia-related conditions, brain inflammation, and Huntington's disease.

"Bringing our organizations together accelerates both companies' strategic plans and creates a biotechnology device leader with the products, pipeline, infrastructure, and financial resources to grow faster and create sustainable shareholder value beyond what either company could achieve separately," said William N. Plamondon III, Chief Executive Officer of Protein Polymer Technologies.

Thuris has received 510k FDA clearance for a non-invasive medical device, the NeuroGraph, which assists in the diagnosis of neurological and psychiatric disorders over a broad range of brain-related conditions. The device is based on Electroencephalogy (EEG) and Event Related Potentials (ERP) and includes proprietary statistical learning methods. The software advances allow the device to function as a powerful clinical development tool and psychiatric diagnostic aid. The ERP procedure creates characteristic brain waves that can be used to distinguish healthy from unhealthy function. Thuris plans on marketing the NeuroGraph to pharmaceutical companies for enrollment and endpoint monitoring in CNS clinical trials. The NeuroGraph will also be marketed to neurologists, psychiatrists, and other physicians involved in CNS diagnosis and treatment.

The merger is expected to enable the companies to significantly accelerate their strategic plans, diversify their product portfolios and revenue bases, and further broaden their respective therapeutic device programs.

"Both operationally and culturally, this combination is a great fit. By combining the resources of the two companies and the expertise of the two management teams, we believe that our NeuroGraph medical device will be more expeditiously commercialized," stated Keith B. Hoffman, PhD, Chief Operating Officer of Thuris. "In addition, this merger will enable us to aggressively advance our lead pharmaceutical compound into clinical trials."

Any transaction is subject to the negotiation and execution of a definitive merger agreement acceptable to both parties. Under the proposed terms of the contemplated transaction, a wholly owned subsidiary of Protein Polymer would be merged into Thuris. As a result, Thuris would become a wholly owned subsidiary of Protein Polymer. The stockholders, option holders, and warrant holders of Thuris would receive a number of shares of common stock, or common stock equivalents, of Protein Polymer, equal to between 30% and 50% of the outstanding capital stock of Protein Polymer calculated on a fully diluted basis. As a result of the transaction as currently contemplated, the stockholders, option holders, and warrant holders of Protein Polymer would continue to hold between 50% and 70% of the outstanding capital stock of Protein Polymer, calculated on a fully diluted basis, predicated on a tentative $19 million valuation of Thuris, and depending upon the average trading price of Protein Polymer common stock for the 20 trading days ending 1 day prior to execution of the definitive agreement.

Protein Polymer Technologies, Inc. is a biotechnology company that discovers and develops innovative therapeutic devices to improve medical and surgical outcomes. The company focuses on developing technology and products to be used for soft tissue augmentation, tissue adhesives and sealants, wound healing support, and drug delivery devices. Protein Polymer Technologies' proprietary protein-based biomaterials are uniquely tailored to optimize clinical performance and contain no human or animal components that could potentially transmit or cause disease.

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Benchmarking Drug Delivery – Business Development Resources

By: Josef Bossart, PhD

BIOGRAPHY

Josef Bossart, PhD is a Principal with Bossart4 Bioconsult (www.b4bio.com) and Senior Director at The Sage Group, consulting practices that provide strategic and transactional advice to healthcare companies in the drug delivery and biopharmaceutical fields. Dr. Bossart has more than 25 years of global biopharmaceutical experience in the areas of business development, strategy, and operations as well as sales and marketing. His biopharmaceutical company experience includes executive positions at Enzon Pharmaceuticals and GeneMedicine Inc. He has spent 15 years within the Rhône-Poulenc Rorer group, holding a series of senior positions, including Managing Director of US Ethicals and Vice President of Business and Marketing Development for the RPR Gencell division. Dr. Bossart earned his PhD in Medicinal Chemistry from the Ohio State University, College of Pharmacy. He is a regular contributor to the business development column of Drug Delivery Technology magazine.

You're sitting at a senior management staff meeting and the discussion goes something like this. CEO to the VP Clinical Research, "How is the pivotal trial going for ABC-423?" The VP responds, "We're a little behind, but the CRO and I have agreed that we should open a couple more sites; they expect to have them up and running within a couple of weeks. We should be able to get back on track by the end of the quarter." The CEO then turns to the VP of Human Resources and asks, "How are we doing with recruiting for the new head of research?" The VP responds, "I have three proposals from executive recruiters. I'll be reviewing them later today and have a recommendation for your approval by tomorrow. They are all expensive, but I'm confident we can have a person onboard within 3 months." Concerning legal issues, the General Counsel offers, "We have outside counsel working on redrafting the manufacturing agreement. It will be ready by the end of next week. The patent application on our newest lead is being drafted by our IP firm and should be ready at the same time." The CFO chimes in, "Our investment bankers are preparing the offering memorandum; we'll have a copy to review by Thursday."

The CEO turns to you, the head of business development and asks, "Where are we with partnering for ABC-423? Are you going to be able to have a signed term sheet by the end of the quarter as we promised the Board?" How you respond will depend on the resources you have allocated to finding and signing up a corporate partner. You'd like to be able to say, "We have two interested parties to date, and due diligence with the first company starts early next week. At the same time, we will be actively following up with the rest of our target group. By the end of this month, we should have five companies heading to due diligence. I'll be floating draft terms sheets to these companies by the end of next month." Or you might answer, "We're a bit behind. I've had to split my time between the partnering program and getting ready for our upcoming strategic planning meeting. I'm also having trouble targeting the right people at the companies and getting them to return my calls and e-mails."

How you respond will most likely depend on the resources you have available. Your management team colleagues know that they can't do it all themselves. Would your VP of Human Resources cold call potential management candidates at other companies? Does your Head of Development contact clinical sites to see if they would be interested in participating in a clinical trial?

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DO YOU WANT A CONSULTANT OR SERVICE PROVIDER?

Let's start with a consultant joke. The chickens in a large hen house have started to quarrel, wound each other, and many of them die every day. The upset farmer hurries to a consultant, and asks for a solution to his problem. "Add baking-powder to the chickens' food," says the consultant, "it will calm them down." After a week, the farmer comes back to the consultant and said: "My chickens continue to die. What shall I do?" "Add strawberry juice to their drinking water, which will help for sure." A week passes, and again the farmer comes to the consultant: "My chickens are still quarrelling. Do you have some more advice?" "I can give you more and more advice," answers the consultant. "The real question is whether you have more chickens."

Many companies and individuals providing business development services will label themselves as consultants. A quick online survey of 15 groups providing business development services found 12 referred to themselves as consultants. A similar review of legal firms found that none of them were self-labeled consultants; even though a large part of their business is counseling clients on what and what not to do. Do biopharma companies hire clinical research organizations to consult on clinical trials? Well, yes and no. There is consulting, but as a necessary part of conducting the clinical trial. Your clinical research colleagues are much less interested in being told what to do than in having help to get it done. Everyone would be better served if business development "consultants" more correctly referred to themselves as business development service providers.

BUSINESS DEVELOPMENT NEEDS

So with more work on your plate than you have the resources to handle, you start to wonder exactly how business development service providers (BDSPs) can help. But exactly what do you need? Beyond responsibility for securing and managing partnerships, do you prepare product forecasts and product opportunity assessments, draft product labeling and positioning, in-license technologies, prepare premarketing materials, conduct market research, or prepare business plans? And if you are part of a smaller organization, are you actively involved with public relations and financings? It can make sense to get help in areas where you have less hands-on experience, the cost of failure is high, or where the required resources are greater than you can assemble within your department or company.

Increased resources do more than help ensure success, they can provide for better outcomes. Partnering is a good example. The quality and timeliness of a deal is dependent on the number of potential partners you have in the queue. As with real estate, the more people you have interested, the greater the likelihood you will receive an offer; even multiple offers. Unlike real estate in a hot market though, you can't just put your property on a multiple listing service and wait for potential buyers to arrive. You need to identify potential partners and reach them with a strong message. Do you have the time and experience to get the partnering process started? Can you access the best prospects? Do you have the resources to manage interested parties while continuing to reach out to new prospects? Just because you have a nibble on the line doesn't mean you should stop casting out other lines in search of additional prospects; there may be an even bigger fish waiting to be caught. And what about valuing the deal? Do you have the experience to be sure that the fish on the line is the biggest one you can catch? Having more lines and more hands can mean more bites, which makes it easier to pull out a winner.

BUSINESS DEVELOPMENT SERVICES

What kind of business development services can a BDSP deliver? Each group will have their particular strengths, but in general, they can provide a full range of services from strategy to tactics to logistics and implementation. Areas of expertise can range from partnering to marketing and market research to merger and acquisition to in- and out-licensing to intellectual property to forecasting and valuations. Unlike most biopharma companies, these business development service providers will handle multiple projects throughout the course of a year. This means they already have key contacts and data sources in hand, as well as proprietary tools, such as spreadsheets for forecasts and valuations. Working on multiple deals also means that these groups will have good insights into current partnering dynamics as well as state-of-the-art analytical tools.

BENEFITS & LIABILITIES OF EXTERNAL BUSINESS DEVELOPMENT SERVICES

Arguably, the most important benefit of engaging a BDSP is expertise, experience, and the additional "hands and heads" they bring to your project. And BDSPs are a resource you pay for only when needed, and only for as long as needed.

These services of course are not free. The first question I hear from many clients after they accept the benefits of looking outside for help is, "How much?" Prices can seem high when compared to having a similar resource in-house. But when adjusted for the duration of need and the expertise provided, the service can be very cost effective. Few companies outside of Big Pharma and Big Bio can rationalize "owning" rather than "renting" this type of expertise and service.

WORKING WITH A BUSINESS DEVELOPMENT SERVICE PROVIDER

Clear objectives are crucial to ensuring success when working with a BDSP, regardless of the project scope or objectives. Objectives will define deliverables, timing, and the resources required to be successful.

Are you looking at a project that involves providing a market evaluation for a new product? Or is it a review and recommendation of strategic options for the company? For these types of projects, the objectives and timelines are relatively easy to define, and the BDSP should be able to quote a fixed-fee price, based on the scope and timeline of the project. A fixed-fee approach has the benefit that both parties know what is to be delivered, when, and at what cost.

For projects where the project is open ended and directly related to time spent by the BDSP, the best approach is generally a time-based fee arrangement. This will most often involve a fixed hourly or daily fee with time dictated by the project demands. Common assignments involving this arrangement include participation in contract negotiations, the review of contract terms, or participation in due diligence activities. I am sometimes asked to review a term sheet a client proposes to present to a potential partner. With a little bit of review, I am able to point out issues that may be troublesome to their potential partner and offer alternate solutions. For assignments like this, I'll charge on the basis of the actual time spent reviewing the documents and preparing my comments. This is similar to the pricing approach adopted by many attorneys for the drafting of agreements or negotiation involvement, and rates are comparable.

A blend of a fixed and success fee is appropriate for projects that involve securing development partners or licensees, and where the objectives are more challenging and outcomes are not ensured, regardless of ability and effort. The fixed service fee component might involve a monthly fee for the duration of the project, while the success fee, generally the larger portion, is paid only upon successful execution of the project.

For success-fee-based projects, the question often arises as to whether the BDSP will forego the service-fee component and work solely for a success fee. It's a fair question. If the BDSP is that good, then they should be willing to defer payment, outside of expenses, to success. No success, then no reward. Not many BDSPs will consider this type of arrangement for the simple reason that the BDSP has no authority to consummate an agreement. Success is dependent on the client's approval, which can be withheld for many reasons unrelated to the performance of the BDSP. One company I worked with confessed to me that they had previously engaged a BDSP to license out a product on a success-fee-only basis. The BDSP delivered a deal within the defined parameters, but didn't receive a success fee because in the interim, the Board decided on a new strategic direction that did not involve out-licensing the product.

While the client defines the scope of any project, and the service provider defines its fee, there is always room for discussion, on both objectives and fees. Alignment of interests can often be reached by redefining the project, the fee structure, the responsibilities, or the timeline.

REFLECTIONS

You're sitting at the management meeting and your CEO looks at you and says, "While I'm happy that our partnering deal was completed as promised, the business development expenses are over what was forecast in the annual budget." You look at your CEO and apologize for the oversight, and to ensure it doesn't happen again, promise to budget for help next year. It's much easier taking credit for reaching your objectives and apologizing for a budget overrun than it is taking credit for being under budget but falling short of your objectives. The obvious solution is to budget for the help you need to reach your objectives. Your management colleagues wouldn't have it any other way. ♦

Should the Molecule Dictate Drug Delivery?

By: Contributor Cindy H. Dubin

In the movie *The Day After Tomorrow*, the world ignored the warnings of a pending climate change and disaster ensued. The same can be said for the pharmaceutical industry. A climate change is underway and industry is turning the other cheek, according to Ian Wilding, PhD, Scientific Advisor at UK-based Pharmaceutical Profiles. Consider the facts: The number of new drugs being developed is flat, which potentially equates to flat revenues; development costs are at an all-time high; and drug failure rates are soaring (75% of drugs don't succeed). Actually, only 1 in 11 drugs in Phase I trials make it to market and of those that make it to market, only 1 in 3 cover the full development costs.

Often, the industry looks to drug delivery systems as a powerful, cost-effective strategic marketing tool to differentiate products, develop superior drugs with significantly improved therapeutic benefits, extend product life-cycles, and remain competitive. These technologies are a cost-effective resource that give pharmaceutical companies competitive and financial advantages, and provide patients with improved medications, according to a report from Penwest Pharmaceuticals.

The secret to weathering the storm, said Dr. Wilding, is to be realistic about the molecule being developed and the boundaries that may exist when it comes to selecting a drug delivery technology for that molecule. "Drug delivery companies ideally want their technology utilized by as many in the pharma industry as possible, but the technology should not be forced onto every molecule," said Dr. Wilding. "Tailor the delivery technology to the molecule. Industry needs to look at a molecule's needs and not its wants." This is what Dr. Wilding describes as "molecule pull vs. technology push."

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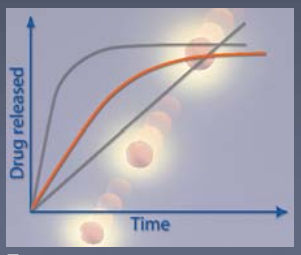

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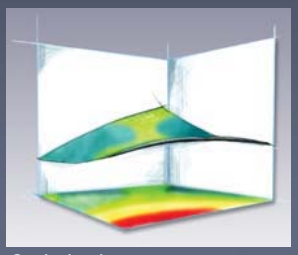
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FIGURE 1

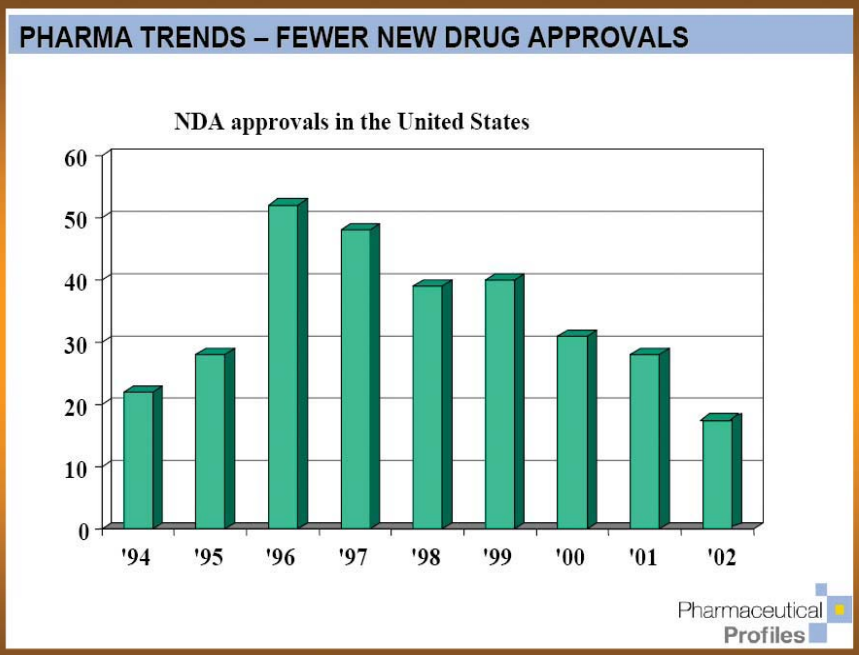
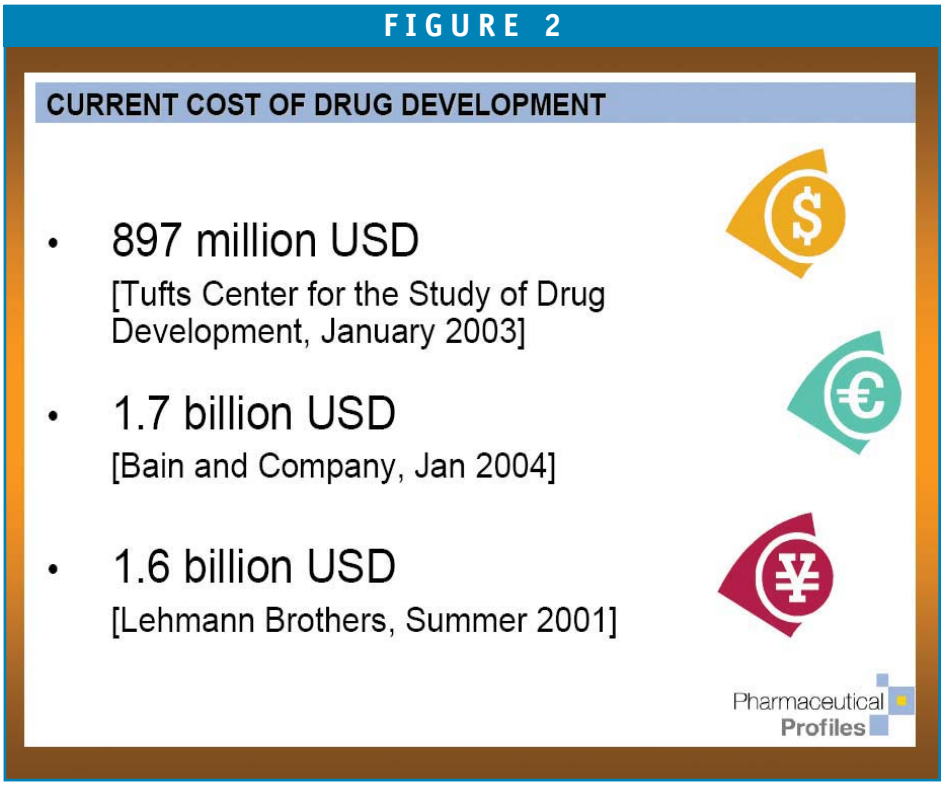


FIGURE 2



IS DRUG DELIVERY SELLING OUT?

In their efforts to thwart generic competition and maintain above-average margins, branded pharmaceutical companies are finding drug delivery technology so valuable that they have partnered with or acquired drug delivery companies. Consider when Johnson & Johnson once indicated that 11 times revenue was a fair price for drug delivery technology when it paid $10.5 billion for Alza, the largest drug delivery company at the time. Drug delivery companies stand to profit from Big Pharma's difficulties by selling themselves to branded drug companies or by selling their technologies through lucrative licensing deals, according to a report from Raymond James & Associates, Inc.

"Typically, Big Pharma is less willing to take risks when it comes to drug delivery," said Dr. Wilding. "The thinking is that new drugs are adverse to new drug delivery technologies."

While Big Pharma tends to focus on proven drug delivery systems — taking very little risk into unchartered territory — the biotech industry is more willing to take on non-validated technologies. Because biologics can be more difficult to deliver successfully into the body due to their larger size and protein make-up, biotechs are looking to the drug delivery sector to develop new, more convenient ways of administration.

TECHNOLOGICAL LIMITATIONS

For patients, advances in drug delivery improve the pharmacoeconomics of drugs by reducing adverse effects; identifying new indications; simplifying the dosing regimen and administration; and improving therapy, safety, efficacy, convenience, and compliance, according to the Penwest report. These improvements, in turn, bolster patient compliance, which improves outcomes and quality of life and reduces costs and frequency of caregiver visits.

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[i] Wiess, P.M., http://www.femalepatient.com/html/arc/sig/pharma/articles/028_07_031.asp

The dual chamber cartridge shown is a Vetter Lyo Cartridge (V-LK®).

Vetter Lyo Cartridge is a trademark of Vetter Pharma.

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FIGURE 3

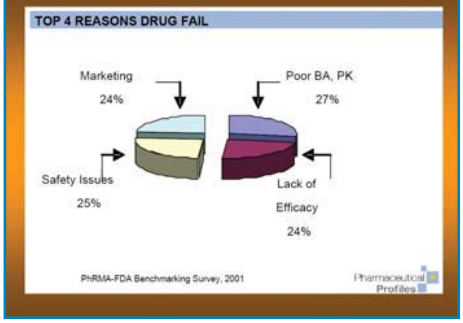
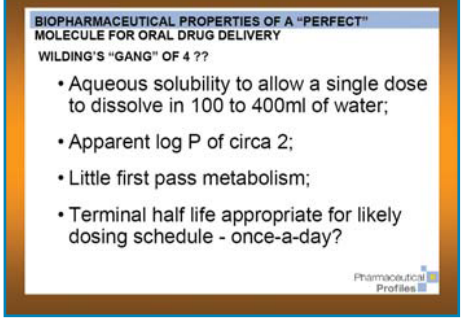


FIGURE 4



Commercially, delivery technologies give new life to drugs, repositioning them with a new or improved therapeutic benefit and a competitive edge. By extending the product's life-cycle with a line extension, they sustain the drug's market value.

While Dr. Wilding agrees that drug delivery can enable the success of a molecule, he believes that technology can only go so far. "The biggest challenge industry faces today is selecting the right delivery solution. A molecule works best with technology if the relationship between the two is symbiotic. Some technology can work wonders with a molecule, but we are not magicians and can only work with what we have."

And what industry has possibly should be taken into consideration as early as the point of molecule discovery. According to the Medical Device & Diagnostic Industry (MDDI), a drug delivery device design should be an integral part of the entire product development process. While drug manufacturers typically focus predominantly on development of the medication, the delivery component is often overlooked until late in the development process. Therefore, delivery manufacturers must communicate the importance of involving the design team early and often throughout the drug's development. MDDI's position is that a successful drug delivery device can become more than a tool for accurately administering medication. It can turn a good medication into a blockbuster.

THE GSK WAY

Dr. Wilding recommends implementing drug delivery early into the research phase of drug development. Critical here is to consider the science of the molecule and design delivery potential into the molecule.

At GSK, Pharmaceutical Development plays a key role in the development of new medicines. In the early stages of the drug development process, the group provides the scientific expertise needed to support the assessment of a drug substance's potential for further development. Pharmaceutical Development is then responsible for the design of the pharmaceutical dosage form, such as an injectable, inhalation, or oral formulation, and works to enhance the safety, efficacy, and ease of use of the medicine. Finally, Pharmaceutical Development manufactures, packages, and supplies products to support clinical trials. The group also determines and plans the manufacturing processes needed to ensure that GSK can supply a medicine to patients once regulatory approval is granted.

Scientists working in Product Development design and formulate new tablets, capsules, injections, ointments, and intranasal sprays. One of the most effective methods for treating diseases of the lung, such as asthma or chronic obstructive pulmonary disease, is by delivering the medicine directly to the lung. This is achieved by creating medical devices that allow the patient to inhale the required amount of medicine in an aerosol. The development of inhalers that can produce such aerosols is the focus of Inhaled Product Development. This work requires input from multidisciplinary teams containing pharmacists, material scientists, analytical and physical chemists, physicists, industrial engineers, and designers. For this reason, the team is organized into separate units that have responsibility for the different aspects of product development. They include Inhaled Science and Technology, Device Technology, Early Inhaled Development, Dry Powder Inhaler Product Development, and Metered Dose Inhaler Product Development.

EARLY INDICATORS

While pharma prefers tablets and capsules, the reality is that many drugs' developability properties are not ideal for oral administration. As a matter of fact, Dr. Wilding claimed that more than 90% of new drugs have low solubility or poor intestinal permeability. Or both! This is problematic given that molecules are becoming more complex to avoid existing patent libraries. The result is that these drugs are likely to be eliminated from the body via liver or intestinal metabolism.

Dr. Wilding said that human absorption studies provide a mechanism for examining attrition based on developability properties and should be a routine part of early clinical development research. "Discovery produces molecules with improved pharmacodynamics, but suboptimal developability properties," he said.

Human absorption studies are being undertaken to provide a "route map" for the development of molecules with complex biopharmaceutical properties. Dr. Wilding said these studies are a proven approach for fast-tracking drug development. Possible designs for human absorption studies include: 1) Evaluating absorption from key regions of the human gut (Proximal jejenum, distal ileum, ascending colon); and/or 2) Assessing the effect of possible "enabling technologies" on drug absorption from specific regions of the gut.

Data obtained from human absorption studies provides early insight into the developability properties of a new drug, which ultimately determines the potential for successful development. Dr. Wilding said, "These studies establish realistic boundaries and manage expectations about what science and drug delivery can do." ♦

FIGURE 5

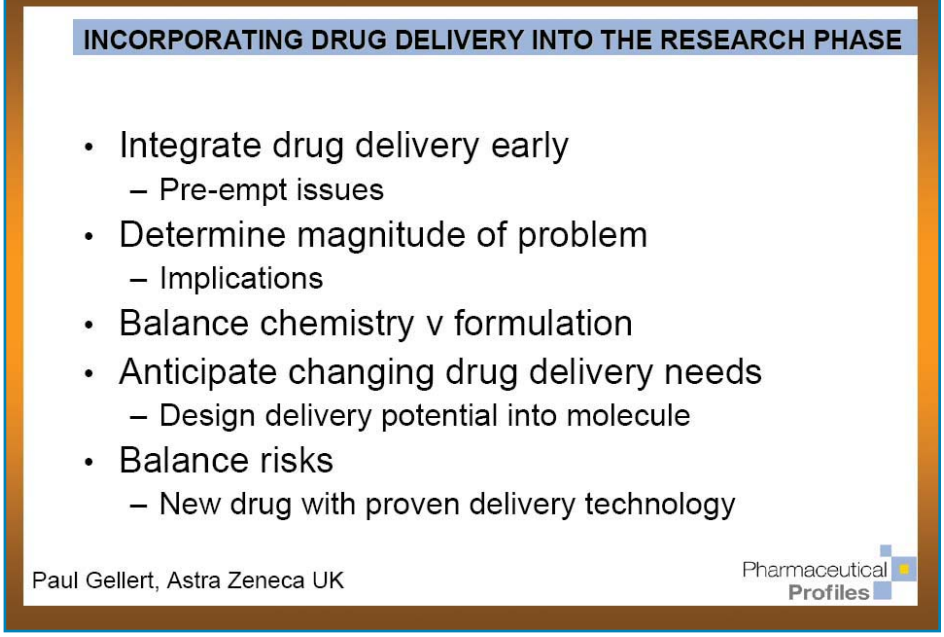
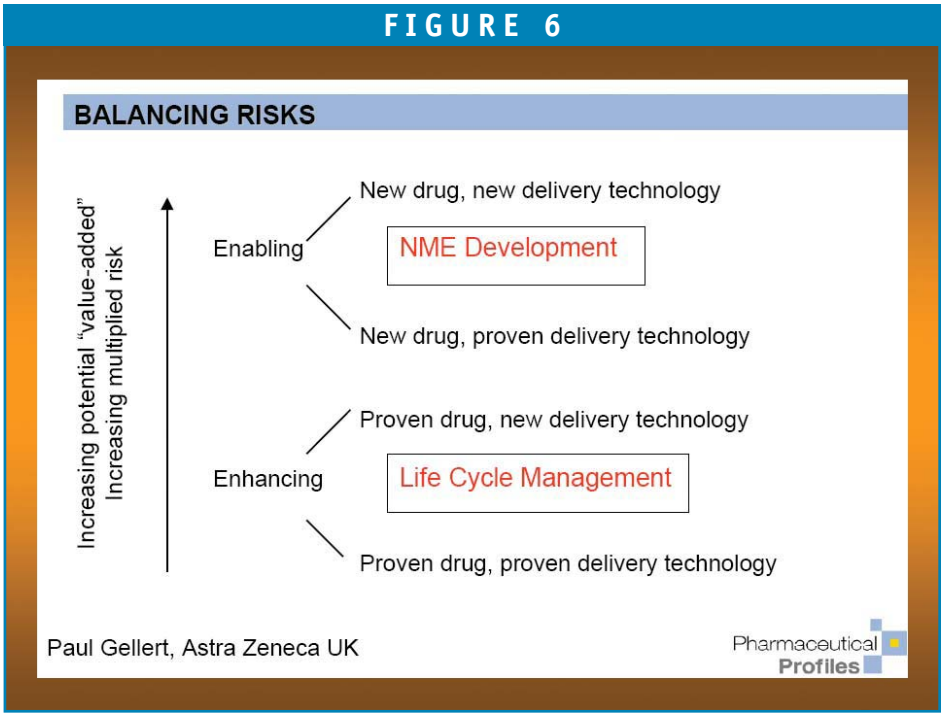


FIGURE 6



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 this position, 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. Ms. Dubin earned her BA in Journalism from Temple University in Philadelphia and a certificate in Business Logistics from Pennsylvania State University.

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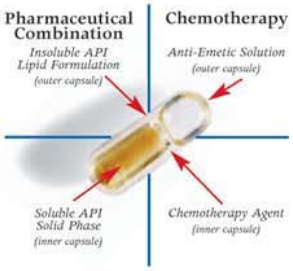

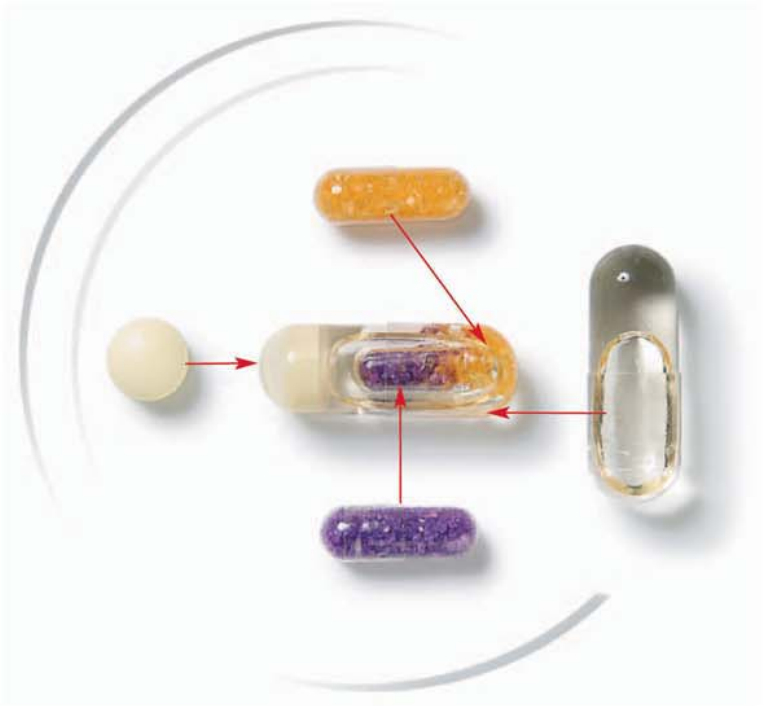

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Patent Infringement – Understanding Patent Claims

By: Clifford M. Davidson, Esq.

BIOGRAPHY

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

Many of you have had the opportunity to review patents as a step in product design or strategic planning. Perhaps you have reviewed a patent in the hope of determining for yourself whether or not you had a patent infringement problem. However, reviewing a patent without first having a basic understanding of how to review it is not particularly useful, and could be dangerous. The following will provide the reader with a basic review of patent claim analysis.

The first step in evaluating a patent claim is to understand that it is only the patent claim(s) that define what a patent actually covers.[1] In many circumstances, the information found before the patent claims, ie, the specification of the patent, is much greater in scope than the actual granted property right. A patent claim may be independent (defining the property right in of itself; claim 1 is always an independent claim) or dependent (meaning that it refers back to a previous claim, and includes some further limitation or restriction). Needless to say, it is only necessary to infringe one claim of a patent, either an independent claim or a dependent claim – a product doesn't have to fall within every claim to have a patent infringement concern.

Patent infringement analysis center around the determination of whether a product or method in question infringes a patent claim. In order to assess the applicability of the claims of a patent to a product or a method of manufacture, patent attorneys follow the general procedure of (i) considering the ingredients or components of the product and/or its method of manufacture; (ii) consider the legal requirements for claim interpretation, and interpret the claims based on these legal requirements; then (iii) compare the product/method to the properly interpreted claims of the patent; and finally (iv) determine whether an issue of infringement exists.

A claim may be infringed in two ways: a) literally or b) under the doctrine of equivalents. For a claim to be literally infringed by an accused product or method, every limitation set forth in a claim must be found in an accused product [or method], exactly. See *Southwall Technologies v. Cardinal IG Co.,* 54 F.3d 1570, 1575 (Fed. Cir.), *cert*. denied, 516 U.S. 987 (1995)(citations omitted). For a claim to be infringed under the doctrine of equivalents, the accused product must contain elements identical or equivalent to each claimed element of the patented invention. See *Warner-Jenkinson Co. v. Hilton Davis Chem. Co.,* 520 U.S. 17, 29 (1997).

In reviewing patent claims, the meaning of the words and phrases used in those claims must be considered. The words used in the claims are generally accorded their ordinary or accustomed meaning unless it appears that the inventor used them differently. See *Envirotech Corp. v. Al George, Inc.,* 730 F.2d 753, 759 (Fed. Cir. 1984). Almost without exception, it is the case that during a patent litigation the

meaning of specific words and phrases in one or more of the patent claims will be disputed by the parties. The patentee/owner will attempt to ascribe one meaning to the claims, while the defendant will ascribe a different meaning, each party understanding that the meaning of the disputed words or phrases adopted by the court may very well be a determining factor in determining whether the disputed product infringes the patent. The determination of the meaning of the words and phrases of the claims (referred to as "claim construction") is often made during a pretrial hearing conducted by the court, which is referred to as a "Markman Hearing" after the court determination in *Markman v. Westview Instruments, Inc.,* 52 F.3d 967, 976 (Fed. Cir. 1995), aff'd, 517 U.S. 370 (1996). Once the court has determined the meaning of the claims, a fact finder (ie, the jury in a jury trial or the judge in a bench trial) will then analyze whether the accused device falls within the scope of the properly interpreted claims. See *Id.* at 976; *Standard Oil Co. v. American Cyanamid Co.,* 774 F.2d 448, 452 (Fed. Cir. 1985).

How does the court determine the meaning of the claims? There are some basic rules that are worthy of discussion.

THE ROLE OF INTRINSIC EVIDENCE

In interpreting the claims of a patent, the judge will look to the claim language itself, to the patent specification and the prosecution history of the patent. *Markman,* 52 F.3d at 979. The patent specification may serve as a dictionary, which explains the invention and may define terms used in the claims. Id. In addition, the prosecution history may be used to clarify what the patentee meant by certain claim terms. In interpreting claims, the words of a claim are typically given their ordinary and customary meaning to a person of ordinary skill in the art, at the time of the invention, and after reading the entire patent, including the specification, and prosecution history, ie, the intrinsic record. *Phillips v. AWH Corp.,* 415 F.3d 1303 (Fed. Cir. 2005).

Most recently, the Federal Circuit held that in performing claim construction, primacy should be given to the intrinsic evidence of record, which is more reliable than extrinsic evidence as an interpretative aid. *Id.* The claims do not stand alone, and must be read in view of the specification, of which they are a part. *Phillips,* 415 F.3d at 1315. The specification may reveal a special definition given to a claim term by the patentee that differs from its ordinary meaning, or may reveal an intentional disclaimer, or disavowal, of claim scope by the inventor. *Id.* at 1316. Indeed, the specification "is always highly relevant to the claim construction analysis. Usually, it is dispositive; it is the single best guide to the meaning of a disputed term." *Id.* at 1315 [quoting *Vitronics Corp. v. Conceptronic, Inc.,* 90 F.3d 1576, 1582 (Fed.Cir.1996)]. However, when a patentee clarifies the meaning of various claim terms to overcome rejections applied by the Examiner, the clarification becomes part of the prosecution history and can be used by a judge in claim interpretation. See *Markman*, 52 F.3d at 980. Indeed, the law is clear that "when multiple patents derive from the same initial application, the prosecution history regarding a claim limitation in any patent that has issued applies with equal force to subsequently issued patents that contain the same claim limitation." *Biovail Corp. Int'l v. Andrx Pharms., Inc.,* 239 F.3d 1297, 1301 (Fed. Cir. 2001), quoting *Elkay Mfg. Co. v. Ebco Mfg. Co.,* 192 F.3d 973, 980 (Fed. Cir. 1999).

THE ROLE OF EXTRINSIC EVIDENCE

A judge, in his or her discretion, may also consider extrinsic evidence, which aids in the interpretation of the claims, in addition to the patent specification, and/or the prosecution history. See *Markman*, 52 F.3d at 980-81. Extrinsic evidence consists of all evidence external to the patent and prosecution history, including dictionaries, treatises, and expert testimony. See *Phillips v. AWH Corp.,* 415 F.3d at 1317 (citing *Markman*, 52 F.3d at 980). The role of extrinsic evidence in claim interpretation is limited: This evidence is not for the purpose of clarifying ambiguity in claim terminology. It is not ambiguity in the document that creates the need for extrinsic evidence but rather unfamiliarity of the court with the terminology of the art to which the patent is addressed. See *Markman*, 52 F.3d at 986; *Vitronics*, 90 F.3d at 1584. For example, while a judge may use expert testimony to help understand an unfamiliar term of art, expert testimony cannot be used as extrinsic evidence to clarify any ambiguity in the document. However, if an analysis of the patent and its prosecution history is sufficient to "resolve any ambiguity in a disputed claim term… it is improper to rely on extrinsic evidence. Vitronics, 90 F.3d at 1583. Further, the Federal Circuit cautioned that while "extrinsic evidence may be useful to the court, [] it is unlikely to result in a reliable interpretation of patent claim scope unless considered in the context of intrinsic evidence." *Phillips*, 415 F.3d at 1319.

Nevertheless, "it is entirely appropriate, perhaps even preferable, for a court to consult trustworthy extrinsic evidence to ensure that the claim construction it is tending to from the patent file is not inconsistent with clearly expressed, plainly apposite, and widely held understandings in the pertinent technical field." *AFG Indus. v. Cardinal IG Co.,* 239 F.3d 1239, 1249 [(Fed. Cir. 2001) (*quoting Pitney Bowes, Inc. v. Hewlett-Packard Co.,* 182 F.3d 1298, 1309 (Fed. Cir. 1999)].

COMPARISON TO THE PROPERLY INTERPRETED CLAIMS

The proper interpretation of the claims marks the beginning of the infringement analysis. As previously mentioned, a claim may be infringed in two ways: a) literally or b) under the doctrine of equivalents. In the infringement analysis, the focus is on a comparison of the (accused) product/method with the claims.

For a claim to be literally infringed by an accused product or method, every limitation set forth in a claim must be found in an accused product [or method], exactly. *Southwall Technologies v. Cardinal IG Co.,* 54 F.3d 1570, 1575 (Fed. Cir.), cert. denied, 516 U.S. 987 (1995)(citations omitted).

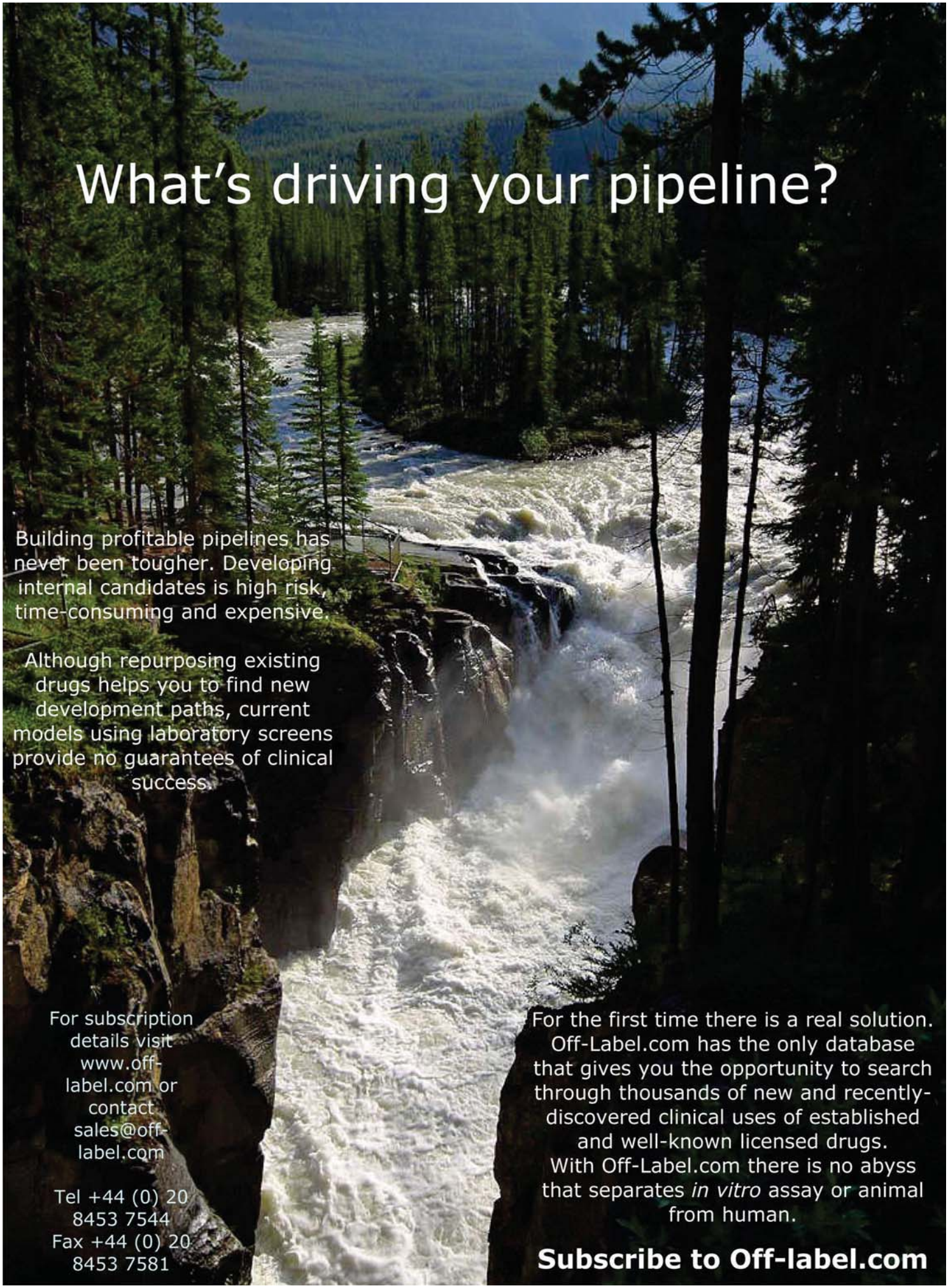
Even if there one determines that there is no literal infringement, there may still be infringement if the accused product contains "elements identical or equivalent to each claimed element of the patented invention." *Warner-Jenkinson Co. v. Hilton Davis Chem. Co.,* 520 U.S. 17, 29 (1997). The Court of Appeals for the Federal Circuit has noted that "[A] claim element is equivalently present in an accused device if only 'insubstantial differences' distinguish the missing claim element from the corresponding aspects of the accused device." *Sage Prods. v. Devon Indus.,* 126 F.3d 1420, 1423 [(Fed. Cir. 1997) (citing *Hilton Davis Chem. Co.,* 62 F.3d 1512 (Fed. Cir. 1995)]. The Supreme Court has noted that the doctrine of equivalents cannot be "allowed such broad play as to effectively eliminate [a claim] element in its entirety." *Warner-Jenkinson,* 520 U.S. at 29. Thus, the accused device must include each claimed element, either the literal element or an equivalent of that element. However, the doctrine of equivalents may not be used to broaden the scope of the claim to encompass what was already in the public domain, ie, found in the prior art. *Wilson Sporting Goods, Co. v. David Geoffrey & Assoc.,* 904 F.2d 677 (Fed. Cir.) cert. denied, 498 U.S. 992 (1990), overruled on other grounds, *Cardinal Chem. Co. v. Morton Int'l.,* 508 U.S. 83 (1993). Importantly, the U.S. Supreme Court has further held that an amendment narrowing the scope of a claim for any reasons related to patentability will create a prosecution estoppel. *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.,* 535 U.S. 722 (2002). Moreover, once an estoppel is created, there is a presumption that prosecution history bars a finding of equivalents for the amended claim element, and the patentee bears the burden of showing that the amendment does not surrender the particular equivalent in question. *Id.*

SUMMARY

One of the purposes of this discussion is to convince the reader that there are a lot of issues that go into the analysis of whether a patent is relevant to, eg, a product. The issues are complex, and taking short-cuts in the analysis is a risky business. Patent litigation in the pharmaceutical field tends to be more lengthy and even more costly than other technologies. It is highly recommended that when faced with such a situation, the reader obtain the advice and assistance of patent counsel early during product development in order to maximize its chances for successfully navigating around or through patent litigation. ♦

REFERENCES

1. Patent claims are found at the end of the patent, and are always numbered and preceded by a clause that states something to the effect "What is claimed is:".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CONTROLLED RELEASE

Asymmetrically Coated Tablets

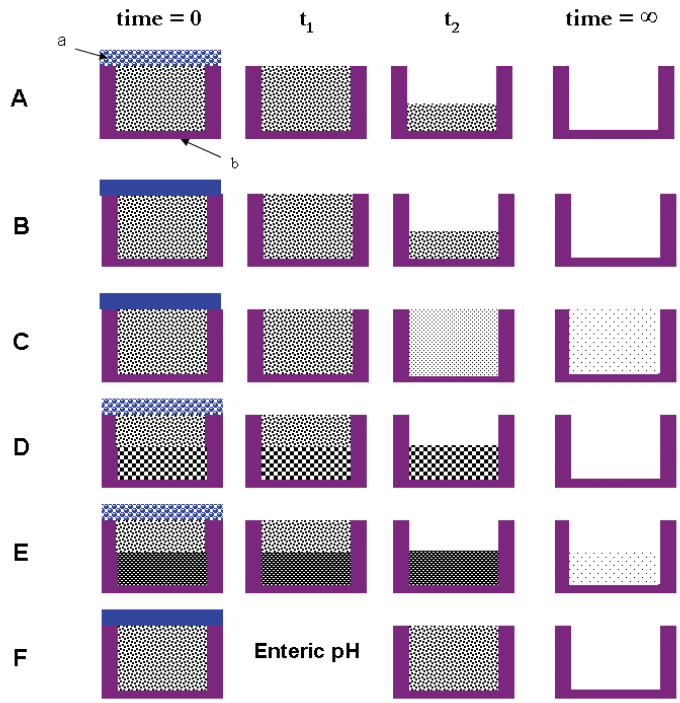
By: Cherng-ju Kim, PhD

ABSTRACT

Asymmetrically coated tablets (ACTs) are developed so that immediate- or time-delayed times can be precisely controlled, and the controlled-release core may provide zero-order or first-order extended and pulsatile release depending on the excipients used in the tablet formulations. The core of the tablet is coated with an asymmetrical coating, that is, a coating with regions having different properties. The coatings may include drugs in varying concentrations. Further, different regions of the coating may have different rates of dissolution. The core of the tablet may be provided with a constant cross-sectional area along a longitudinal length of the tablet, a coating having a first region with a more rapid rate of dissolution than a second region. The dissolution of the first region exposes only the cross-sectional area to the dissolution medium. The second region of the coating prevents any other portion of the core of the tablet from being exposed to the dissolution. Therefore, because the cross-sectional area remains constant as the core is dissolved, the rate of release of the drug from the core of the tablet remains constant. The cross-sectional area may be of any geometrical configuration so long as the area remains constant as the core dissolves. Comparative results of ACTs and commercial brand products are presented.

FIGURE 1

Asymmetrically Coated Tablets



INTRODUCTION

There are many controlled-release dosage forms (CRDFs) marketed today.[1] There are several benefits to using CRDFs over conventional dosage forms: reduction in drug blood level fluctuation, improvement of patient compliance, reduction in local or systemic effects, etc.[2] However, CRDFs allow pharmaceutical companies to extend the life cycle of their pharmaceutical products beyond the chemical patent life of a drug. These products are produced by using various mechanistic principles: matrix controlled, membrane-reservoir controlled, swelling controlled, polymer dissolution controlled, osmotically controlled systems, etc.[3,4] Each system provides unique release kinetics. Many companies produce their CRDFs by using one or more principles. However, each technology may deal with a few drug candidates because of drug solubility, drug loading level, choice of drug carriers, and manufacturing processes, etc. Thus, pharmaceutical companies try to develop and maintain several controlled-release technologies.

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FIGURE 2

Release of Metoprolol Succinate from ACTs and Toprol® XL

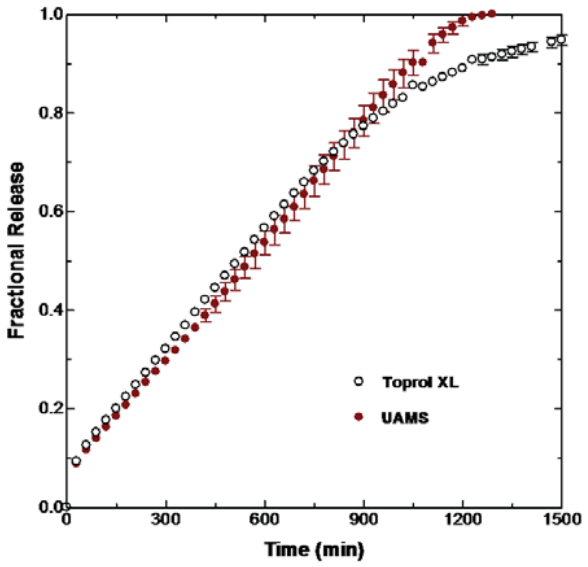
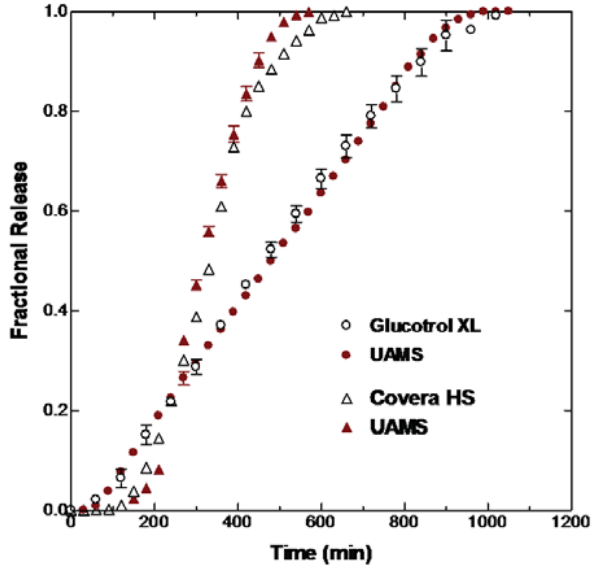


FIGURE 3

Release of Glipizide & Verapamil HCl from ACTs & Glucotrol® XL & Covera® HS



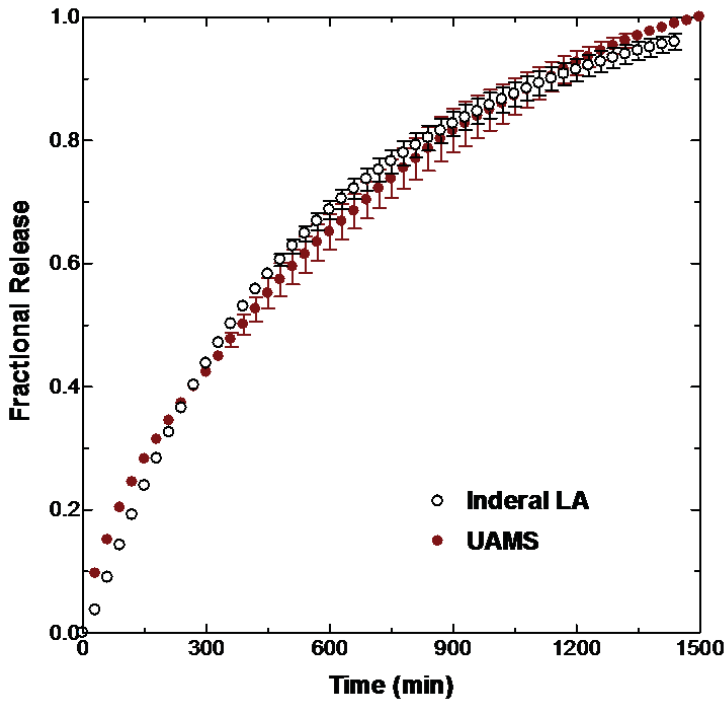
While constant drug-release rates are desirable in certain circumstances, it is more generally desirable in order to customize the kinetics of drug release. For example, a rapid initial release (a burst) may desirably be followed by a period of constant release. In other examples, it might be desirable to delay the release of the drug for a period of time or to release a pulse of the drug after a period of constant release. In order to obtain immediate release followed by controlled release or time-delayed release followed by controlled release or time-delayed release by pulsatile release, dosage forms (eg, tablets) have been coated uniformly with appropriate coating excipients with or without drugs dispersed in the coating. When the coating layer disappears (or dissolves), the controlled release "tablet shape," which has the combined geometry of a slab and a cylinder, is exposed to the dissolution medium than thus the same kinetic problems of other dosage forms, where a surface area accommodating drug release decreases with time and the diffusional time of a drug from a diffusing front becomes longer with time, are encountered. In this article, a controlled-release technology called asymmetrically coated tablets (ACTs) is introduced in order to yield various drug-release profiles for a variety of drugs. With the ACT technology, one may achieve precisely controlled immediate-release or time-delayed release times, and the controlled-release tablet may provide zero-order or first-order controlled release and pulsatile release, depending on the excipients used in the tablet formulations. Controlled-release kinetics can be manipulated as a dosage form designer wishes.

ASYMMETRICALLY COATED TABLETS (ACT)

Figure 1 illustrates a variety of asymmetrically coated tablets. The core of the tablet of ACT is coated with an asymmetrical coating, which is a coating with regions having different properties. The coatings may include drugs in varying concentrations. Further, different regions of the coating may have different rates of dissolution. In one example of the ACT, the core of the tablet is provided with a constant cross-sectional area along a longitudinal length of the tablet. So long as only the cross-sectional area is exposed to the dissolution medium, zero-order release kinetics; ie, a constant release rate, may be achieved. This is accomplished by providing the tablet with a coating having a first region with a more rapid rate of dissolution and a second region. The dissolution of the first region exposes only the cross-sectional area of the core to the dissolution medium. The second region of the coating prevents any other portion of the core of the tablet from being exposed to the dissolution medium, at least until the core of the tablet is dissolved. Therefore, because the cross-sectional area remains constant as the core is dissolved, the rate of release of the drug from the core of the tablet remains constant. The cross-sectional area may be of any geometrical configuration so long as the area remains constant as the core dissolves.

FIGURE 4

Release of Propranolol HCl from ACTs & Inderal® LA



Case I: Burst Release Followed by Controlled Release

Figure 1A shows the tablet with two coating regions, a first region (Figure 1A-a) comprising a water-soluble polymer, eg, hydroxypropylmethylcellulose (HPMC), hydroxypropyl-cellulose (HPC), polyethylene glycol (PEG), etc, and a second region (Figure 1A-b) comprising a water-insoluble polymer, eg, ethyl cellulose. Alternatively, the first region may comprise a water-soluble polymer, and the second region may also comprise a water-soluble polymer, where the first region has a greater rate of dissolution than the second region. The first region of the coating incorporates a drug so that the rapid dissolution of the first region provides a burst release of the drug. With the dissolution of the first region, the core is exposed to the dissolution medium, and the drug begins to be released at a constant rate. Figure 2 shows the release of metoprolol succinate from ACTs superimposed on the release of the drug Toprol® XL. When the release of a drug from the core of the tablet is controlled by the erosion of polymer, eg, hydroxypropylmethylcellulose acetate succinate (HPMCAS), the release kinetics are expressed in the following equation:[5]

Equation 1.

$$\frac{M_t}{M_\infty} = \frac{k_e}{l} t$$

Where M_t and M_∞ are the amount of the drug release at time t and the total amount of the drug in the ACT, respectively, and k_e and l are the erosion rate constant and the thickness of the core, respectively.

When there is a diffusional contribution toward the overall release kinetics in addition to the erosion of polymer, the release kinetics is expressed by the following equations:[6]

Equation 2.

$$\frac{M_t}{M_\infty} = \left(\frac{4Dt}{3l^2}\right)^{1/2} + \frac{k_e}{l} t$$

for a dissolved drug

Equation 3.

$$\frac{M_t}{M_\infty} = \left(1 - \frac{1}{2}\frac{C_s}{A}\right)\delta + \frac{k_e}{l} t$$

for a dispersed drug

Where D and δ are the diffusivity of the drug and the dimensionless diffusion layer thickness, respectively, and C_S and A are the drug solubility and drug loading, respectively. When the polymer employed swells and erodes, eg, HPMC and polyethylene oxide (PEO), etc, Equations 2 and 3 become the following equation:[7]

Equation 4.

$$\frac{M_t}{M_\infty} = \alpha\sqrt{t} + \beta t$$

Where α and β are associated with a drug diffusion and polymer erosion, respectively. In general, the first term of the right-hand side of Equations 2, 3, and 4 becomes small when either the drug solubility or drug loading (eg, <50%) are low.[8] Even if a drug diffusion occurs, drug-release profiles can be shown as the first-order kinetic behavior at early time for a short period of time followed by zero-order kinetics.

FIGURE 5

Release of Venlafaxine HCl from ACTs & Effexor® XR

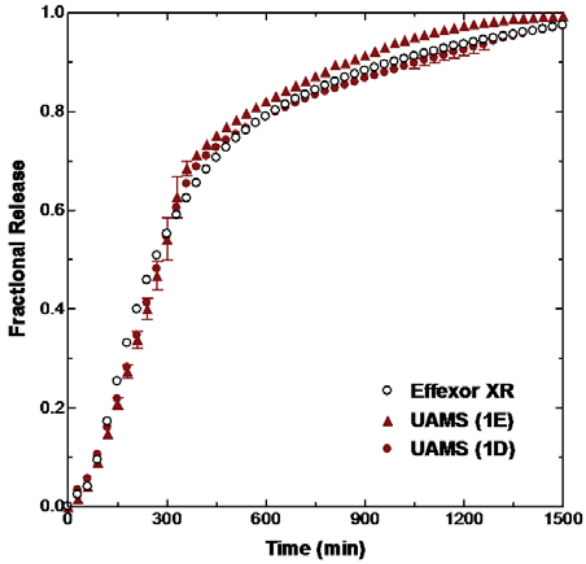
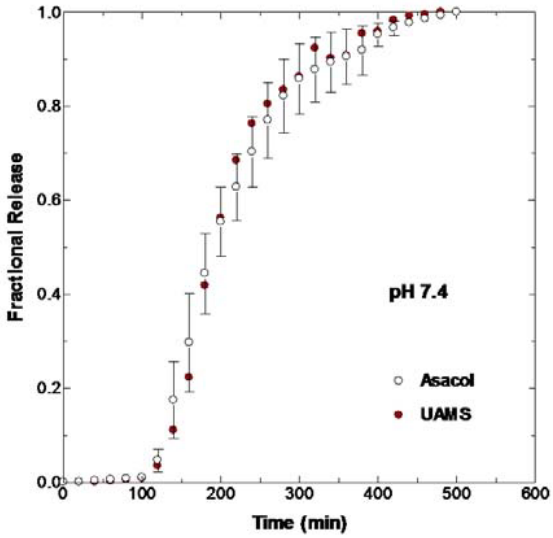


FIGURE 6

Release of Aminosalicylic Acid from ACTs & Asacol®



Case II: Time-Lag Followed by Controlled Release

Figure 1B shows the tablet with two coating regions like Figure 1A. However, the first region may comprise a water-soluble polymer without incorporating a drug. The rate of dissolution of the first region is selected so that the release of the drug from the core is delayed for an interval of time. The delay may be determined by the thickness of the first region or by selecting water-soluble polymers for the first region having greater or lesser molecular weight. When the first region dissolves, the core (eg, HPMC, HPC, HPMCAS, PEO, etc) is exposed to the dissolution medium, and the drug begins to be released at a constant rate as expressed by the aforementioned equations. Figure 3 shows the release of glipizide and verapamil HCl from ACTs superimposed with the commercial products Glucotrol® XL and Covera® HS, respectively.

Case III: Fickian Controlled Release

Figure 1C shows the third design of the ACT. This is similar to the designs of Figures 1A and 1B, but the core of the ACT is made with a water-insoluble polymer (eg, ethyl cellulose) rather than the water-soluble polymers of Figures 2 and 3. By the use of water-insoluble polymers, the rate of the drug release is determined by Fickian kinetics as expressed by the following equation:[9]

Equation 5.

$$\frac{M_t}{M_\infty} = 1 - \frac{8}{\pi^2}\sum_{n=1}^{\infty}\frac{1}{(2n+1)^2}\exp\left(-\frac{D(2n+1)^2\pi^2}{4l^2}t\right)$$

Because only the cross-sectional area of the core is exposed to the dissolution medium unlike regular tablets, a very high loading (eg, > 50%) thin core tablet can be formulated. Figure 4 shows the release of propranolol HCl from ACTs superimposed on the release of the drug Inderal® LA. In this example, the first coating region allows a slightly delayed release.

Case IV: Sigmoidal Release

Figures 1D and 1E show the embodiments of the fourth and fifth ACT. Unlike the embodiments described in Cases I to III, the embodiments of Figures 1D and 1E have a core formed in two parts. The two parts are formulated to give two different release rates for the drug. For one example, the rate of drug release from the first part is set to be greater than the release rate from the second part; however, the present design contemplates that either part may have greater rates than the other. The first coating region may allow a burst-release or time-delayed release like Cases I and II or a combination of both. Further, any number of parts may be employed as a particular situation requires. For the other example, a drug from the first part made of water-soluble polymers is released at a constant rate followed by a Fickian release from the second part made of water-insoluble polymers. Figure 5 shows the release of venlafaxine HCl from ACTs superimposed with the release of the drug from Effexor® XR. In this example, the rate of dissolution of the first

region is selected so that a very slow release over a short time occurs in the release of the drug from the first part of the core. The release of the drug from the first part of the core is shown by the initial steep linear release in the fractional release. The slope of the first part is dependent on the choice of water-soluble polymers. When the first part of the core has been completely dissolved, the second part begins to dissolve at a less rapid but essentially linear rate until the drug from the second part is completely dissolved. One may observe a middle, transitional (curved) release between two linear releases. The combined transitional release and late release portion can be achieved by Fickian release kinetics from the second part made of water-insoluble polymers. Different release rates of the drug may be accomplished by the initial concentrations of the drug in each part or by varying the excipients.

Case V: Pulsatile Colonic Delivery

Unlike Figures 1A through 1E, in this design (Figure 1F), the first coating region is made of an enteric polymer that is soluble at an enteric pH of 5.0 and higher. There is no drug release as long as the ACT remains in an acidic environment (ie, stomach). Depending on the thickness of the polymer in the first region, the dissolution of the first region is delayed until the tablet has exposed to an enteric pH for a given period of time. For example, one can deliver a drug in the colon (not the small intestine) by adjusting the thickness of the first region. After the dissolution of the first region, the core dissolves at the predetermined rate. The predetermined rate is dependent on the choice of water-soluble excipients and the solubility of a drug. Figure 6 shows the release of aminosalicylic acid from ACTs superimposed on a graph of the release of a commercially available brand of Asacol®. Due to the solubility of the drug, the release is not as rapid as a dosage form designer wishes.

CONCLUSIONS

The present CRDF has been described with certain preferred and alternative designs of ACTs. Various combinations of the designs described can be employed to design a dosage form for whatever release kinetics are desired. Further, although the designs described herein relate to a dosage form having zero-order kinetics, the present ACT is not so limited. Other applications can be found elsewhere.[10] And ACTs can be commercially manufactured by a three-step process or one-step process.[11]

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BIOGRAPHY

Dr. Cherng-ju Kim joined the faculty in July 2004 as Associate Professor of Pharmaceutical Sciences, UAMS College of Pharmacy, Little Rock, Arkansas. Dr. Kim earned his BEng in Chemical Engineering from Korea University in Seoul, Korea, his MEng in Environmental Engineering from Manhattan College in Riverside, NY, and his PhD in 1984 in Chemical Engineering from McMaster University in Hamilton, Ontario, Canada (Polymer Reaction Engineering). After working in industry for several years, he became a Research Associate in the Faculty of Pharmacy at the University of Toronto and subsequently joined the School of Pharmacy at Temple University in Philadelphia as an Assistant Professor. He was promoted to Associate Professor and Director of Graduate Studies at that institution in 1998 and served in those roles until 2002 when he moved to Loma Linda University School of Pharmacy as Associate Professor and Chair of Pharmaceutical Sciences. Dr. Kim has received several Teacher of the Year awards at Temple and Loma Linda. His primary research interests include the development of polymeric materials for controlled-release drug delivery systems and the modulation of drug release kinetics. As the author of Controlled Release Dosage Form Design and Advanced Pharmaceutics: Physicochemical Principles, he published more than 60 papers and 5 patents in this field. His innovative controlled-release technology at Temple University eventually led to fruitful results and reached a major licensing agreement with a pharmaceutical company (the largest licensing agreement in Temple University technology transfer history at that time). Recently at UAMS, he has reached a licensing agreement with a foreign pharmaceutical company.

Timing Drug Availability With Therapeutic Need

By: Troy M. Harmon, MS, MBA, Senior Director, Business Development, Eurand, Inc.

INTRODUCTION

The Specialty Pharmaceutical marketplace continues to expand across many fronts: Companies specializing in developing products for specific patient populations, such as pediatrics or geriatrics; companies focusing in niche therapeutic areas; and drug delivery companies utilizing proprietary technology bases to create unique pipelines. The success of the Specialty Pharma industry segment is evidenced by the steady increase in the number of Specialty Pharmaceutical products that have been brought to market. There are significantly more new drug products approved compared to the approval of new chemical entities (NCEs) (Figure 1); two-thirds of NDAs are for line-extensions and/or new formulations of already marketed drugs. Likewise, the number of Specialty Pharma "blockbuster" products with >$500 million in annual sales is on the rise — a 250% increase in the past 7 years to more than 50 such products last year (Figure 2).

In many cases, Specialty Pharma companies are taking advantage of the risk/reward benefits of reformulation of already approved drugs with known safety profiles and shorter development cycles. The bread-and-butter of Specialty Pharmaceutical product development relies on minimizing the risk of drug product development. Big Pharma needs NCEs to drive growth and keep generic competition from destroying brand value; however, small and mid-size companies can reap significant reward from reformulation projects that provide for an unmet need — greater convenience, fewer side-effects, innovative use of off-patent drugs in new indications or in combination products. Frequently, Specialty Pharma will turn to drug delivery technology companies to provide creative approaches to developing their new products — needleless injection, transdermal patches, nasal and lingual sprays. In the oral drug delivery field alone, there are companies offering technologies for gastroretention (when the absorption window is a concern) or lipid-based formulations to enhance bioavailability or pulsatile release to create custom pharmacokinetic profiles.

However, the gold standard for route of administration remains oral delivery, preferably once-a-day administration, and pulsatile and/or delayed-release technologies can be used to enable qd dosing for challenging drug substances. Specifically, with regard to delayed or pulsatile drug delivery, there is an opportunity to develop specialized "chronotherapeutic" products to time the release of drug at the optimal time-of-day.

CHRONOTHERAPY

Most physiological, biochemical, and molecular processes in healthy organisms display robust, predictable changes on a 24-hour schedule. Chronotherapeutic products can synchronize drug delivery with circadian rhythms in order to optimize efficacy and/or minimize side-effects. This is one avenue to extend the useful life of a drug substance and create new brands for Specialty Pharma — a less expensive development proposition with potentially higher returns given the time to develop a product based on an NCE or even a combination product for a new indication.

The outdated western theory of "homeostasis" taught that the probability of risk or intensity of disease was equal throughout a specific period. However, chronobiology (the quantitative study of the rhythmic temporal relationships of biologic phenomena) has quite clearly been proven across many biological functions:

- *Intraocular Pressure (IOP)* — in glaucoma patients IOP peaks at 4 AM and has a trough in the afternoon, opposite that of people with normal IOP;
- *Hormone Secretion* — growth hormone and melatonin are produced at night; testosterone and cortisol in the early morning hours;
- *Allergic Response* — skin tests produce a 3X greater result when given at night;
- *Gastric Motility* — slower at night, which can impact controlled-release product design;
- *Seasonal Affective Disorder (SAD)* — affects 1% to 3% of adults; increased sleep and appetite are a well-known phenomena in winter;
- *Atrial Fibrillation* — hospital admissions peak in April with a trough in August;
- *Blood Coagulation* — even with constant heparin infusion rate, thromboplastin time and risk of bleeding vary significantly during the day;
- *Cholesterol Production* — statins dosed in evening have been shown to be more effective;
- *Asthma Treatment* — evening dosing can improve lung function during sleep; and
- *Cancer Drug Administration* — treatment timing can significantly reduce side-effects.

FIGURE 1

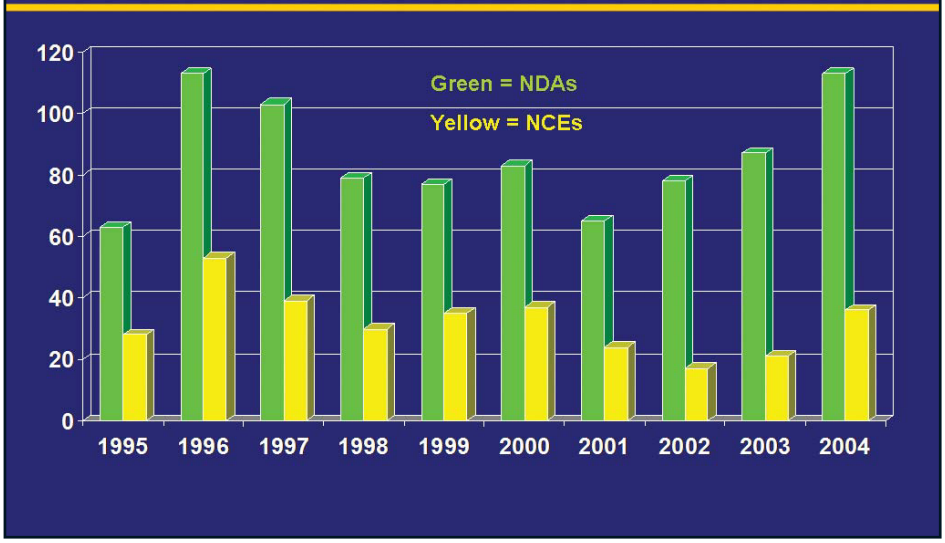
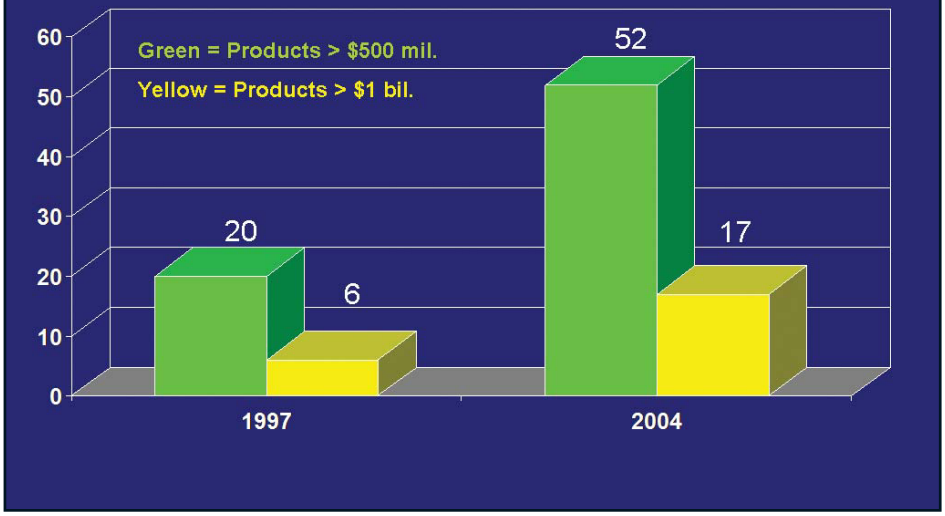


FIGURE 2



For diseases ranging from asthma to arthritis, the cure may be dictated by the timing of drug administration. Hence the emergence of chronotherapy — coordination of medical treatment with biological rhythms is especially useful for disease states with known circadian patterns. Chronotherapy has been appreciated in the principles of eastern medicine for a long time, but drug development is just now catching up. By taking advantage of known biological patterns in disease manifestation, the goal of developing chronotherapeutic products to optimize the desired effects of a drug and minimize its undesired ones, can be achieved in certain disease states. For example, the benefits of chronotherapy are well established in the treatment of cancer, and the timing of chemotherapy drug administration can improve treatment tolerability and permit higher, more efficacious dosing. The survival rate in ovarian cancer may be quadrupled when doxorubicin is given in the morning and cisplatin in the evening.

Furthermore, there is a high incidence of disease symptoms and adverse events in the morning hours, so ensuring that adequate plasma levels of a drug are present in the morning can be critical to effective treatment of many diseases, including cardiovascular disease (Figure 3). This is also true for pain management — pain in the morning is greatest for some conditions, but evening pain is more common in other conditions. In addition, the more narrow the therapeutic window of the active, the more important the implication of circadian variation in plasma levels. Development of suitable chronotherapeutic oral dosage forms can be achieved using delayed- and/or pulsatile-release technologies.

PULSATILE DRUG DELIVERY

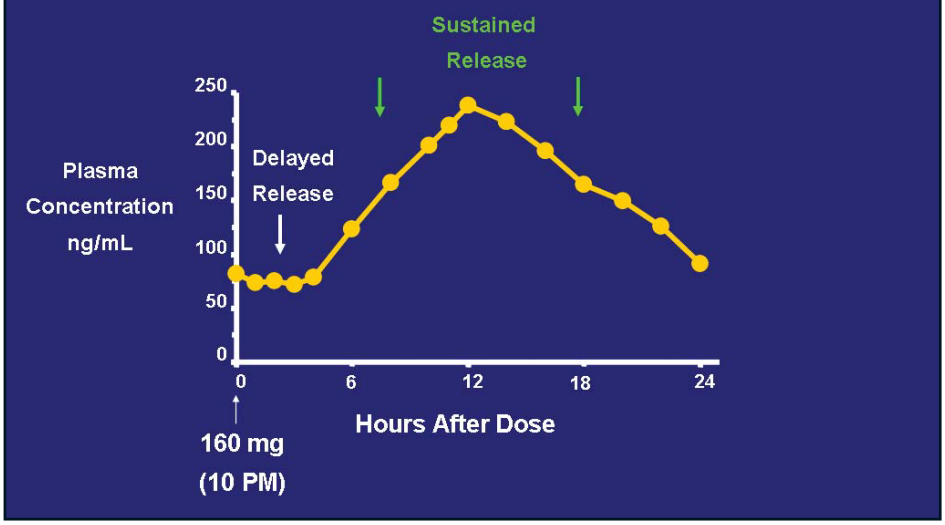
Oral drug delivery technology has been used to enable a number of chronotherapeutic drug products. In the treatment of attention-deficit disorder, it is important to maintain adequate plasma levels during school hours, and, in some cases, have the plasma levels decrease after school hours so that the side-effects of appetite suppression and insomnia are not manifested. There are a couple of methylphenidate products are on the market that achieve this goal, including MetaDate CD®, which releases the methylphenidate in two pulses separated by a delay.

Chronotherapy is important in the GI area — treatment of ulcers and heartburn throughout the day can be improved by timing drug availability before meals as gastric acid secretion increases after a meal. Also, some patients suffer from night-time gastro-esophageal reflux disease (GERD), and a pulsed drug product has been developed to minimize acid secretion during the night. Delayed-release medications for hypertension

FIGURE 3

	Midnight - 6am	6am – Noon	Noon – 6pm	6pm – Midnight
Stroke	18%	37%	26%	19%
Heart Attack	20%	32%	25%	23%
Cardiac Death	19%	33%	26%	22%

FIGURE 4



are prescribed for evening dosing so that adequate plasma levels are available in the morning hours when cardiovascular events are more likely. Covera HS®, Verelan PM®, and InnoPran XL® (Figure 4) are examples of marketed products utilizing this approach.

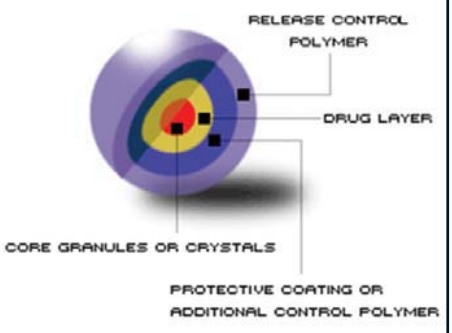
There are a variety of oral dosage form technologies suitable for achieving pulsatile drug delivery: Osmotic-pump systems, erosion-based monolithic tablets, and multiparticulate-containing capsules to name a few. In particular, there are numerous advantages of multiparticulate systems for achieving flexible and accurate pulsatile drug delivery. Multiparticulate dosage forms are composed of small beads, with each bead composed of many layers. Some of the layers contain drug substance, and other layers are rate-controlling polymers (Figure 5).

The beads are typically ≤ 1 mm in diameter and readily disperse in the stomach. Unlike larger tablets, these small beads exit the stomach in a more consistent fashion, thus pharmacokinetic variability is decreased. Also, adjustment of dose strength and creation of dose-proportional products is quite facile with a multiparticulate system. Combination drug products can also be formulated without drug-drug compatibility issues. The range of drug-release profiles is not limited with multiparticulate dosage forms; the dose can be spread over different amounts in two or three pulses, and lag times between pulses can be varied from 1 hour to up to 8 hours. In Figure 6, the drug load is split into two equal parts with the first pulse delivered after the beads have exited the stomach, and the second pulse delivered after a lag time of 6 hours.

SUMMARY

There are several technical challenges that must be overcome to develop chronotherapeutic medicines using pulsatile delivery technology. Ensuring that the drug has an adequate absorption in the lower GI tract is an important consideration. In some cases, it is necessary to conduct in vivo intubation studies before a formulation can be developed. Also, a growing number of drug candidates demonstrate pH-dependent solubility, especially poor solubility at the higher pHs of the lower gastrointestinal tract. By careful choice of the polymer film composition of the bead layers, solubility hurdles often can be overcome. Correlating the pharmacokinetic profile with the pharmacodynamic response is instrumental

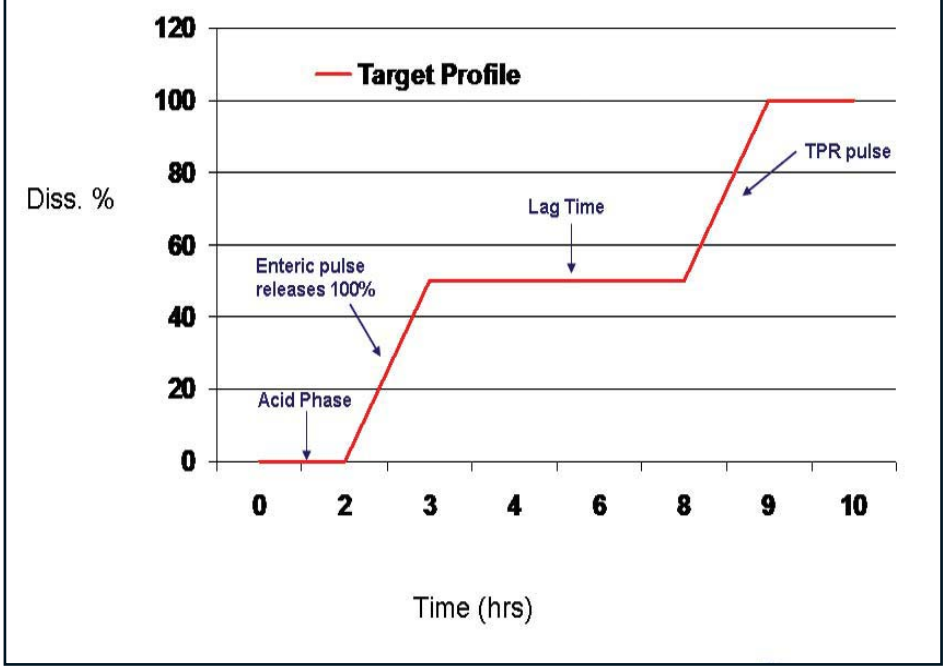
FIGURE 5



in designing the ideal release profile, and whether or not there is significant activity, and circulating plasma half-life, from any metabolites of the active.

Finally, from the regulatory perspective, proof that treatment efficacy is improved by a customized dosing regimen is needed to receive a strong label claim and to get intellectual property protection for an improved formulation. All of this makes development of chronotherapeutic, pulsatile-release products particularly challenging; however, getting the right drug to the right place at the right time can provide competitive differentiation in an increasingly crowded marketplace, where many companies are increasingly developing new formulations of the same drug.

FIGURE 6



BIOGRAPHY

Mr. Troy Harmon is currently a Sr. Director, Business Development for Eurand, Inc., a Specialty Pharmaceutical company focused on the development of novel drug delivery technologies and products. Mr. Harmon joined Eurand in 2002, and his responsibilities include business development, marketing, and licensing efforts for Eurand in North America. Prior to joining Eurand, Mr. Harmon was Director, Business Development at Delsys Pharmaceutical in Princeton, NJ, where he was responsible for marketing and partnering the company's electrostatic powder deposition technologies worldwide. In addition, Mr. Harmon has served as Director, Business and Product Development at FEI Technologies, a company specializing in implantable drug delivery systems, and as Sr. Scientist at Summit Technology, an innovator in laser vision correction procedures. Mr. Harmon earned his BS from the University of Kentucky, where he was elected to Phi Beta Kappa and received the University's first prize for undergraduate academic research. Mr. Harmon also earned an MS in Physical Chemistry from Cornell University, and an MBA from Villanova University.

SENSOR TECHNOLOGY

Liquid Drug Delivery Monitoring & Control

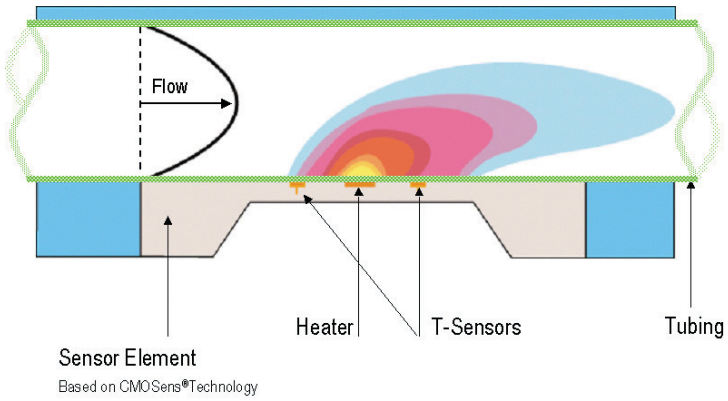
By: Mr. Ulf Kanne

INTRODUCTION

New microchips combining sensor technology with digital signal processing on one single CMOS microchip are boosting performance levels and reducing costs in measurement technology. While a real revolution is already taking place in the market for consumer products using integrated digital CMOS humidity and temperature sensors, disposable digital sensor solutions for liquid drug delivery are becoming available.

FIGURE 1

Principle of Thermal Flow Measurement



Inset 1. Lack of Monitoring Functionality? An example:

X Recalls Infusion Kits

NEW YORK (2004 Reuters Health) –
Medical device maker X said on Tuesday it is recalling Y-Type infusion sets used by (...) because of problems that can interrupt (...) flow and cause serious consequences, including death. The company said patients should exchange any unused Y-Type infusion sets for replacements. X said that the problems that led to the recall have resulted in a number of serious injuries, including some hospitalizations.

CURRENT SITUATION

Product and marketing managers for disposable drug delivery products see various desirable features that are not yet implemented in their products. Improved safety profiles, process monitoring functions (such as detection of clogging or bubbles) and electronic recording of delivered volumes are increasingly being discussed (Inset 1).

Furthermore, progress in pharmaceutical development is leading to increased demand for improved dosing accuracy, which can be achieved by active control of pumping and dosing processes using feedback control.

The key to technical features, such as delivery monitoring and feedback control, are flow sensors that allow flow rates to be measured accurately over the range of millilitres per minute to nanolitres per minute, depending on the application. Continuous measurement of flow over time even allows the total delivered amount of the drug to be calculated.

Sensors for these flow ranges have been commercially available for several years already. However, they have been disqualified due to factors such as high cost, size, and for battery-operated applications, high energy consumption.

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Professor Carl Djerassi


Dr. Joseph Miletich

Measuring the Impact of Innovation in Discovery and Development

KEYNOTE SPEAKERS

Is Innovation Positively or Negatively Impacting Discovery and Development?
Dr. John L. LaMattina, Senior Vice President, Pfizer Inc and President, Pfizer Global Research and Development

Bridging the Industry and Academia Divide to Drive Innovation Forward
Dr. Christopher P. Austin, Director, NIH Chemical Genomics Centre, National Institutes of Health

How is Industry Responding to the FDA's Critical Path White Paper? A 2006 Update
Dr. Janet Woodcock, Deputy Commissioner for Operations and Chief Operating Officer, US Food and Drug Administration

Drug Hunting from a Drug Hunter
Dr. Roger Newton, Senior Vice President and Director, Esperion Therapeutics, a Division of Pfizer Global R&D

Sex in an Age of Mechanical Reproduction: Implications for Drug Innovation
Professor Carl Djerassi, Playwright and Emeritus Professor of Chemistry, Stanford University

Maintaining a Culture of Innovation as the Biotech Industry Evolves
Dr. Joseph Miletich, Senior Vice President, Research and Pre-Clinical Development, Amgen

CONFERENCE SESSIONS:

- Novel Approaches to Target Identification and Validation
- Systems and Pathways Approaches to Drug Discovery
- Innovation Around the Use of Information and Applied Knowledge
- Cell Based and Whole Animal Imaging Strategies
- Virtual Screening and ADME
- Novel Screening Technologies
- New Developments in the Hit to Lead Process
- Hit to Lead: New Technologies and Case Studies
- Innovative Strategies for Building Better In Vivo Models
- Innovation in Biomarker Research, Development and Application
- Enabling Technologies for Candidate Selection
- Enabling Technologies for Clinical Trials
- CNS Models
- Case Studies in Parkinsons, Depression and Alzheimers
- Case Studies in Cardiovascular Disease
- Oncology Models and Clinical Disease
- Recent Developments in Oncology Models
- Case Studies in Oncology
- Emerging Opportunities in China and Traditional Chinese Medicines
- Supporting Innovation Through Outsourcing

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FIGURE 2

Highly Integrated, Digital Flow Sensor Chip

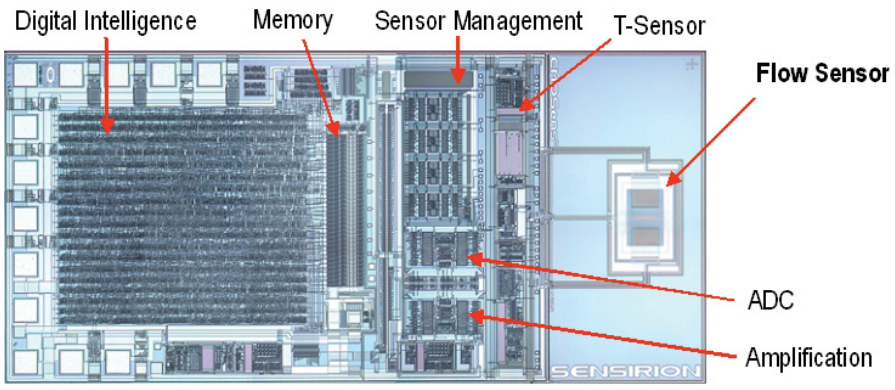
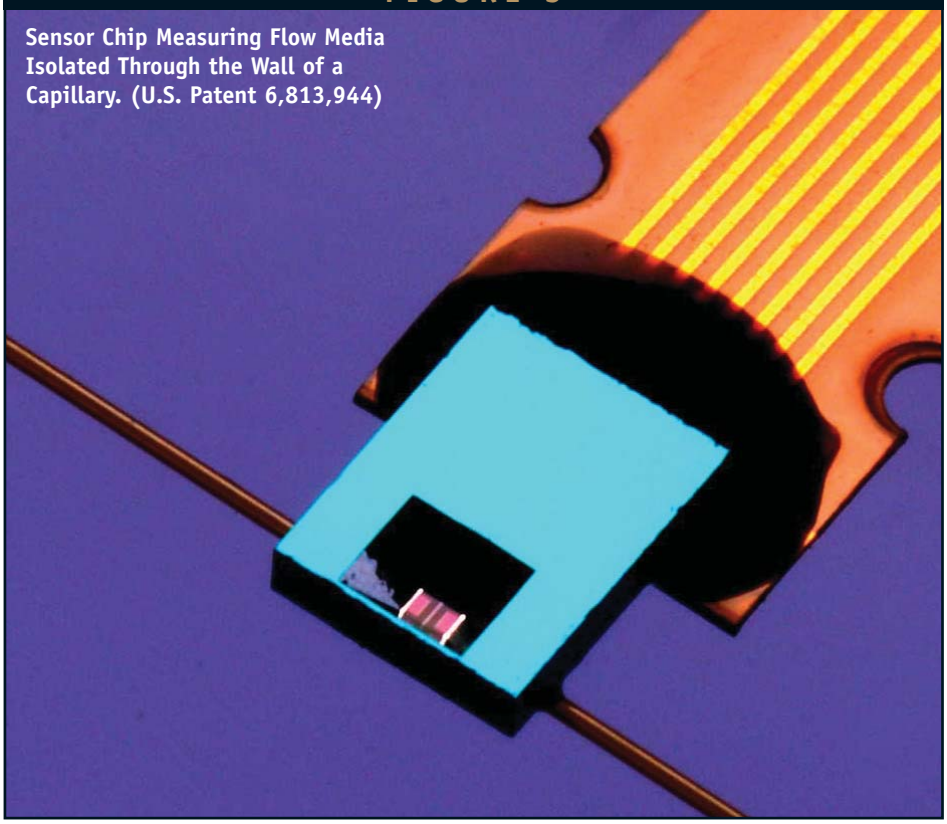


FIGURE 3

Sensor Chip Measuring Flow Media Isolated Through the Wall of a Capillary. (U.S. Patent 6,813,944)



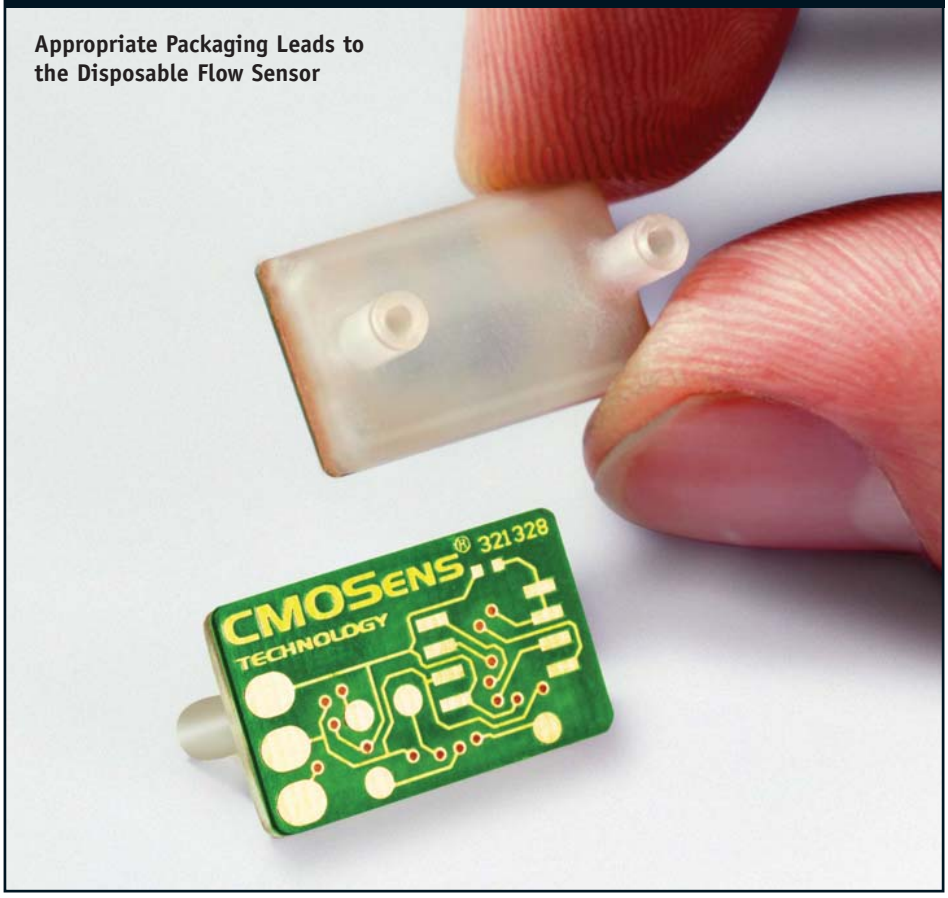
TECHNOLOGICAL PROGRESS

Times have changed, and new sensor generations are appearing on the scene.

What do they look like, and what do they mean for the drug delivery sector? Today, CMOSens Technology is available. It is described as the combination of microsensor technology and digital signal processing on a single CMOS microchip. CMOSens sensors based on MEMS (Micro-Electromechanical System) technology are extremely fast, small, and light, and they can be produced in large quantities. For example, digital CMOSens humidity sensors are being manufactured in quantities of millions per year for consumer applications (Sensirion Inc., Switzerland).

A CMOSens sensor chip for flow measurement obtains its measurement signals from a well-known type of structure (Figure 1). A miniature heating element on the microchip adds a minute amount of heat to the liquid medium for thermal flow measurement. The latest designs can obtain high accuracy using only 90 to 300 micro joule of energy per measurement. Concerns about introducing heat into the medium are thus unfounded in most cases. Two temperature sensors positioned symmetrically upstream and downstream of the heat source detect even the slightest temperature difference, thus providing basic information about the distribution of the caloric energy being transported by the flow. This is the fundamental information needed to subsequently calculate the actual total flow or dosed volume. Additional details of the CMOSens chips (such as a minimized thermal capacity) significantly distinguish these sensors from similar designs and guarantee low power consumption, reliability, and measurement speed (response times < 20 ms). Very high repeatability (approximately 0.6% of the measured value) is an additional benefit of CMOSens flow sensors and by the way a thermal MEMS flow sensor measuring the flow of a liquid is able to detect bubbles therein (see U.S. patent 6,763,710) because the thermal properties of the gas in the bubbles differ from those of the liquid.

FIGURE 4



Appropriate Packaging Leads to the Disposable Flow Sensor

DIGITAL INTELLIGENCE IS THE KEY

A sensor signal must be processed in an appropriate manner to maintain high signal quality and allow them to be integrated into user systems. For most sensors, the essential functions necessary to achieve the high performance required by the application are amplification, digitization, linearization, and temperature compensation. Depending on the MEMS sensor generation (Inset 2), with CMOSens, these functions may be integrated into the sensor chip to provide high resistance to electromagnetic interference (EMC) and superb signal quality at low cost. The structure of such a CMOSens chip can bee seen in Figure 2.

Characteristic sensor data needed for linearization and temperature compensation during operation is generated by a calibration process during production. As freedom from user calibration before initial use is essential for single use sensor solutions, this calibration data must be stored and processed inside the sensor. That is possible in the fourth generation of MEMS sensors. In addition to the actual thermal sensor element, these chips contain the full digital intelligence and even the memory required for signal linearization, temperature compensation, and self-test algorithms.

Achieving this level of integration (a full single-chip solution) is now a reality.

At the same time, a fourth-generation, CMOSens-based MEMS sensor chip for flow measurement is only around 2 X 2 mm in size. Use of standard chip technology makes it possible to produce such sensors at very low cost.

Due to the low energy consumption an interesting option is to provide such sensors with RFID-like on-chip circuitries for wireless communication and/or wireless power supply. Such circuitry can for example comprise a demodulator and rectifier for receiving power and data through a coil antenna as well as a modulator and driver to send back data through the same antenna.

Inset 2. Progress Made in Microsensor Technology

MEMS Sensor Generations

- **1st Generation**
  MEMS sensor element usually based on a silicon structure, sometimes combined with analog amplification on a microchip.
- **2nd Generation**
  MEMS sensor element combined with analog amplification and an analog-to-digital converter on a single microchip.
- **3rd Generation**
  Merging the sensor element with analog amplification, an analog-to-digital converter and digital intelligence for linearization and temperature compensation on a single microchip.
- **4th Generation**
  The same features as third-generation MEMS sensor, plus memory for calibration data and temperature compensation data.

Inset 3. About CMOSens & CMOS

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. Thanks to their compact single-chip design, sensors based on CMOSens Technology have excellent resistance to electromagnetic interference (EMC), which is significant technical advantage of this highly modern sensor technology.

Further reading: www.sensirion.com and Medical Device Technology May 2003 - "Digital CMOS Sensor Chips for Media-Isolated Liquid Flow Sensing."

CMOS (see-mos): is a standard fabrication technology for integrated circuits. CMOS chips are commonly referred to as "semiconductor chips," "silicon chips" or "computer chips." They are widely used in almost all areas of everyday life. The best example of a CMOS chip is probably the Intel Pentium processor in your PC.

ISOLATED MEDIA

Especially in medical and life-science applications, full isolation of the medium from its environment is often required. A surprising solution has been found to achieve this goal. Special packaging enables highly sensitive microchips to measure flow through (thin) walls of PEEK®, steel, or glass with full media isolation. This can be done while maintaining heating power at the same very low level, due to the high sensitivity and signal quality (signal-to-noise ratio) achieved using digital CMOSens chips.

Nowadays, a simple, straight capillary (inner diameter 20 µm to >1 mm) is used as a flow channel for sensors based on this patented principle, with the sensor chip bonded to the outside (Figure 3).

OUTLOOK

This technical development changes the product design ground rules for disposable drug delivery systems. Ultra-small amounts of liquid can now be monitored and dosed with much higher accuracy at low cost. Tiny, fully digital, calibrated flow sensor chips will be part of single use products in the future. As the tiny chips are based on CMOS technology, they can easily be produced in high volumes at low cost in standard semiconductor wafer fabs.

Additional technological issues on the way to single use solutions are packaging (Figure 4) and calibration during production, as well as communication and power supply.

Other issues also become important when the drug delivery system is viewed as a whole. A sensor-actuator combination is needed for most applications, and the actuator must be combined with the sensor and additional components to form a microsystem (such as a disposable dosing unit). The demand for microvalves (active and passive) and micropumps that can be produced in high volume at very low cost will rise significantly in the future. Pumps with no moving parts at all appear to have enormous potential, but even piezopumps and MEMS-based membrane pumps offer attractive features for disposable designs.

The scope of the technical options for increasing the safety and accuracy of drug delivery systems and adding supplementary electronic monitoring and control features has been enlarged significantly. The key are fully calibrated single-chip solutions. Due to the low power consumption and short power-up times of the new sensors, battery-operated systems also benefit from CMOSens Technology, and wireless RFID-like solutions are possible.

The disposable portion of medical solutions will incorporate more functionality in future products. That will make it possible to improve safety and performance while reducing investment and maintenance costs for reusable devices.

Impressive sensor performance (high resolution and high speed at low cost) makes competitive design solutions possible.

Inset 4. Some Potential Liquid Drug Delivery Solutions Based on Thermal MEMS Flow Sensors In Particular Sensors Using CMOSens Technology

A: Combination with conventional gravity-based drug delivery

1. Monitoring the flow of drug for metering and/or recording purposes or to detect leakages, interruption of flow, or bubbles.
2. Controlling flow or dosing of drug with electronic feedback control using a disposable valve or a reusable pinch valve with a disposable tubing.

B: Combination with conventional, reusable (portable or non-portable) drug delivery pump or integration into an implantable pump

1. Monitoring the flow of drug to the human body generated by a peristaltic pump or a syringe pump to the human body for metering and/or recording purposes or to detect leakages, interruption of flow, or bubbles.
2. Controlling flow or dosing of drug with electronic feedback control using a peristaltic pump or a syringe pump as actuator.

C: Combination with a disposable (portable or non-portable) drug delivery pump

1. Monitoring the flow of drug generated by a disposable pump (e.g. membrane pump, electrokinetic pump, or electro-osmotic pump) to the human body for metering and/or recording purposes or to detect leakages, interruption of flow, or bubbles.
2. Controlling the flow or dosing of drug with electronic feedback control using a disposable pump (e.g. membrane pump, electrokinetic pump, or electro-osmotic pump) as actuator.

D: Combination with a physically or chemically pressurized disposable or non-disposable drug reservoir

1. Monitoring the flow of drug for metering and/or recording purposes or to detect leakages, interruption of flow, or bubbles.
2. Controlling flow or dosing of drug with electronic feedback control using a disposable valve or a reusable pinch valve with a disposable tubing as actuator.

E: Pre-dosing of drug into a reservoir before further processing and/or delivery to the body

1. Measuring the flow from one reservoir into another to determine the total amount of liquid moved.
2. Controlling the amount of drug moved from one reservoir into another with flow generated by a disposable pump (e.g. membrane pump, electrokinetic pump, or electro-osmotic pump), with electronic feedback control.
3. Controlling the amount of drug moved from a pressurized reservoir into another reservoir with electronic feedback control in combination with an actuator like a disposable valve or a reusable pinch valve with a disposable tubing.

D: Wireless Applications

The monitoring and control applications according to examples A-E can be extended with wireless transponder technology for the sensor to receive electric energy from and transmit measurement data to a separate control and/or communication unit via an antenna (similar to RFID solutions). This allows to increase comfort for patients and clinical staff and to reduce effort for electrical connections as no batteries and electrical connectors are necessary. Implanted devices measuring the flow of body fluids can benefit in the same way. In portable and non portable systems the wireless readout unit can be positioned in a convenient position in vicinity of the sensor.

BIOGRAPHY

Mr. Ulf Kanne is Product Manager & Sales Director for liquid flow products at Sensirion AG (Switzerland), a leading high-tech sensor company. Throughout the past 4 years. Mr. Kanne has focused on new markets and microsensor applications in the biotech and life science sector as well as in general process technology. Prior to joining Sensirion, he was actively engaged in new technology product management and R&D in the process technology and semiconductor industry for several years. Mr. Kanne studied electronics at the Technical University of Aachen (Germany) and the Federal Technical Institute of Zurich (Switzerland).

CASE STUDY

Partnering With Big-Pharma: Pfizer & CyDex's Positive Experience: A Case Study

By: Contributor Guy Furness

BACKGROUND

For many technology companies, it is a source of eternal frustration that pharmaceutical partners insist on anonymity when they enter into R&D agreements. A pharma company even allowing broad details of the agreement's scope to be printed in the press release announcing it represents a rarely seen gesture to its collaborator.

Yet at the Ninth Annual Drug Delivery Partnerships Conference in San Diego, California, earlier this year, Pfizer's Associate Research Fellow in PRD, Dr. John Crison, took his place on the podium alongside Dr. Diane Thompson, Co-Founder and Chief Scientific Officer of CyDex Inc, to give a joint presentation about the application in life-cycle management strategies of CyDex's drug solubilizing technology.

That corporate-giant Pfizer deigned to co-present with its partner spoke volumes about the long-standing relationship between the two companies. After almost a decade-and-a-half, many real-life lessons have been learned by both parties about how to maintain such a close relationship successfully. Importantly, CyDex has learned how best to fit its crucial partnership with Pfizer with the development of its business independently of this valued partner. Achieving this balance is important for any technology company involved in a major agreement with a large pharma partner, but it is not easy.

Pfizer's relationship with CyDex began back in 1991 when Pfizer UK identified a clinical need for an intravenous infusion of the antifungal compound, voriconazole, which was also being made available as an oral tablet. Although the requirement for an intravenous line extension was clear, the low solubility of voriconazole meant that achieving a concentration high enough for an intravenous dosage form presented a significant technical challenge.

The R&D team knew that cyclodextrins worked well as solubilizing agents for their compound, but hydroxypropyl-β-cyclodextrin (HP-CD) was not available for licensing because a competitor, Janssen, owned it. They therefore needed to find a new solubilizing agent.

THE CAPTISOL® TECHNOLOGY IN BRIEF

CAPTISOL®, the chemical name of which is sulfobutylether 7-β-cyclodextrin (SBE7-β-CD), was invented at the University of Kansas Higuchi Bioscience Center for Drug Delivery in 1990. CyDex, based in Lenexa, Kansas, was founded in 1993 to establish the technology.

Captisol is a donut-shaped molecule with a hydrophilic exterior and a hydrophobic interior. A solid, insoluble drug molecule in an aqueous environment is generally regarded as lipophilic. In the presence of Captisol, such lipophilic molecules readily fit into the lipophilic center or the cyclodextrin molecule to form a 1:1 drug-cyclodextrin complex. The hydrophilic exterior of the complex means that the drug-cyclodextrin complex is water-soluble.

Currently, there are more than 20 open INDs (or equivalents outside the US) for the study of Captisol (two of these are CyDex compounds) and more than 400 pharmaceutical and biotechnology companies are using the technology in the development of their compounds, for delivery via various routes. At the same time, CyDex is progressing toward a specialty pharma model, with multiple Captisol-enabled drug products under development in-house.

PFIZER'S CRUCIAL DECISION

Pfizer quickly identified sulfobutylether 7-β-cyclodextrin (SBE7-β-CD) (CAPTISOL®), under development at the University of Kansas, as the key to enabling its intravenous antifungal to reach the market, where it had the potential for sales in excess of $100 million. However, Captisol was a novel technology in the early stages of development, and therefore carried inherent risk.

It was at this stage that Pfizer made a crucial decision. It weighed up the additional risks and pitfalls of a drug delivery deal and development partnering, which included bringing a new technology forward, against the fact that this technology fitted exactly with the current unmet need. The potential benefits won.

TThe resulting agreement between Pfizer and CyDex, the company which had been spun out of the university to develop the SBE7-β-CD technology, gave Pfizer exclusive rights to antifungals that used SBE7-β-CD and a non-exclusive license to develop other Pfizer compounds using the technology.

The process was to be transferred and scaled up at Pfizer, and the two partners would co-own the manufacturing process and all safety data their collaboration generated. CyDex retained full and independent rights to license its technology to industry.

Dr. Crison explained how, as the alliance grew, the emphasis began to shift from project management toward corporate-scale management. Among the various areas that the partnership's structure had to

TABLE 1

Pfizer & CyDex Both Carried Out Preclinical Captisol® Safety Studies

Pfizer Conducted:	CyDex Conducted:
General Pharmacology	Monkey & Rat Continuous IV Infusion Studies (4-day & 14-day continuous)
Pharmacokinetics & Disposition	Monkey & Mice SC Studies (90-day)
Genotoxicity	Rodent Oral Gavage Studies (1-day, 7-day, 28-day, 90-day)
Bolus IV Rodent Studies (14-day, 30-day, 180-day)	Dog Oral Gavage Studies (1-day, 7-day, 28-day, 90-day)
Bolus IV Dog Studies (14-day, 30-day, 180-day)	Rodent Inhalation Studies (1-day, 7-day, 28-day)
Bolus IV Reproductive Study in Rats & Rabbits (segments I, II & III)	Dog Inhalation Studies (1-day, 7-day, 28-day)

deal with were: IP and patents, legal, regulatory, financial, preclinical and clinical safety, Captisol manufacturing, new technology developments, and line extensions.

Dr. Crison also pointed out that both companies took a major role in most activities. For example, commercial-scale Captisol manufacturing was to be carried out by various companies. Pfizer established manufacturing both in-house and with Abbott; CyDex and Pfizer established manufacturing at 5-10 MT/year with PPG-Sipsy; and CyDex established manufacturing at >50 MT/yr with Hovione. The development of Captisol's preclinical safety package provides another example of how the two partners shared the workload (Table 1).

TANGIBLE RESULTS

In any successful collaboration, a good working relationship between the teams and personnel involved in an alliance is important, and a well thought-out and workable deal structure is of course vital. Another major requirement to ensure a long-lived, happy relationship is that it gets results.

To date, the alliance between Pfizer and CyDex has brought forward two major new Pfizer products, neither of which would have made it to market without the application of the Captisol drug delivery technology.

The first was the formulation of voriconazole that had originally prompted Pfizer to seek a solubilizing technology. It was successfully launched in 2002 as Vfend® IV, and comprises 200 mg of active compound in 16% Captisol at pH 6-7. Pfizer's financial results indicate Vfend (IV + oral) sold $287 million in 2004.

In 2002, Geodon IM (ziprasidone mesylate), the second Captisol-Enabled Pfizer product was launched for the treatment of acute agitation in schizophrenic patients. Dr. Crison said that the original target solubility for the IM formulation was around 40 mg/ml, but that the free base had a solubility in water of 0.0003 mg/ml. The use of a mesylate salt improved solubility in water significantly to 0.9 mg of free base/ml, but still did not bring it close to the target needed for it to represent a viable product. In contrast, using a 40% Captisol formulation, the mesylate salt had a solubility of 44 mg of free base/ml – well within the requirements. The final Geodon IM presentation comprised 20 mg of active compound in 30% Captisol.

MUTUAL BENEFITS IS KEY

Dr. Crison believes that the key to the success of Pfizer's relationship with CyDex is that it is mutually rewarding. Pfizer has gained multiple life-cycle management products, non-exclusive rights to the technology, access to CyDex oral and inhalation data, and CyDex manufacturers.

In exchange, CyDex sealed its first drug delivery systems deal, gained assistance with R&D from a major multinational pharma company, and has been able to use Pfizer's parenteral product data.

It is important to note that although Pfizer could have well afforded to acquire the Captisol technology outright, it only licensed the rights it required. This left the originators of the technology free to explore, research, and develop other applications, thus allowing the technology a chance to reach its full potential both within the realm of Pfizer's activities and beyond.

GROWING AN INDEPENDENT BUSINESS

While the agreement with Pfizer took a central role in the early growth of CyDex and remains central to the company today, it is essential that CyDex, like any company in a similar situation, maintains its independence through the growth of its business outside the partnership.

In fact, the Pfizer agreement plays an important part in making this possible. The first licensee of Captisol being Pfizer, a pharmaceutical giant, validates the technology somewhat, particularly because products have been launched. But in addition to the positive message sent out by having a major player as a partner, there are solid financial benefits. CyDex receives royalties on Pfizer's Captisol-Enabled products, with which it is able to fund the growth of its independent proprietary product development.

This strategy of reinvestment has enabled CyDex to initiate several proprietary product development projects across a range of delivery routes. One example is the application of Captisol in an oral solution. The conventional formulation was high in alcohol and had a bitter taste, and the label calls for it to be diluted in a drink before administration. Whereas the Captisol product was bioequivalent, alcohol free, presented ready to use with no need for dilution, and palatable. In another example of an oral application, Captisol allowed very insoluble compounds that precipitated at pH 6-7, to be formulated as osmotic and polymer-matrix extended-release tablets.

The third example – a nasal line extension of the sedative, midazolam (Versed®) performed at the University of Iceland – illustrated Captisol's application in a different healthcare setting. The nasal route was chosen because the product was targeted for use in the outpatient setting. The onset of action of oral Versed is 40 minutes, which was undesirable for outpatient procedures. Intravenous dosing is often not desirable.

For pulmonary delivery, Captisol has enabled corticosteroids to be formulated as solutions rather than suspensions. Solutions are easier to manufacture and sterilize, and are suitable for use with all types of nebulizers, including ultrasonic nebulizers.

SUMMARY

In summary, CyDex believes that the benefits of forming a close relationship with a major pharmaceutical partner are manifold. Indeed, it is more than simply a belief because they have proof in the form of a successful history, partnered with Pfizer, going back almost a decade-and-a-half. In addition, CyDex has license agreements with an additional 12 big pharma, biotech, and specialty pharma companies. CyDex also has Limited Clinical Use Agreements with 6 of the same group of companies.

Yet, having these relationships need not mean that the technology partner loses its independence. It is crucial for the success of the technology company that its major partner does not hamper growth. Far from inhibiting development, a major partnership should and can represent an enormous advantage. As CyDex and Pfizer have shown, if it is structured and managed well, such a relationship can be leveraged to help build the independent business.

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Currently, there are more than 20 open INDs (or equivalents outside the US) for the study of Captisol (two of these are CyDex compounds) and more than 400 pharmaceutical and biotechnology companies are using the technology in the development of their compounds, for delivery via various routes. At the same time, CyDex is progressing toward a specialty pharma model, with multiple Captisol-enabled drug products under development in-house.

BIOGRAPHY

Mr. Guy Furness is an independent writer specializing in drug delivery. He has had articles on this subject published in various journals, industry magazines, and national newspapers, including four recent publications in The Times newspaper (UK), and has spoken on the subject of drug delivery at international conferences. He is founder of ONdrugDelivery Ltd, a niche industry information company that provides specialist writing and contract publishing services for its industry clients. The company also publishes information on the sector in detailed intelligence reports, and produces bespoke reports for individual clients with particular needs. Prior to ONdrugDelivery, Mr. Furness spent 1 year as a specialist freelance drug delivery writer and, before that, 2 years as Editor of Target World Drug Delivery News, which he helped conceive, set up, and launch in 2001. Mr. Furness began his career as a member of the editorial team of the pharmaceutical R&D products database, Pharmaprojects. He graduated from the University of Bath (UK) in 1998 with a BSc (Hons) in Natural Sciences.

Challenges & Opportunities in Oral Delivery of Poorly Water-Soluble Drugs

By: Chandrashekar Giliyar, PhD; David T. Fikstad; and Shanthakumar Tyavanagimatt, PhD

INTRODUCTION

Advances in molecular biology, emergence of combinatorial chemistry, and innovative high throughput screening has enhanced the output of the drug discovery effort, but has resulted in more poorly water-soluble drugs in the pharmaceutical pipeline. Currently, more than 40% of the marketed drugs are poorly water-soluble, and more than one-third of the drugs listed in the US Pharmacopoeia are poorly water-soluble.[1]

Oral products for poorly water-soluble drugs are frequently plagued with a number of limitations, including the following:[2]

1. Highly variable oral bioavailability (eg, amprenavir, etoposide, dutasteride, amiodarone)
2. Sensitivity to fed-fasted state, and meal content and timing (atovaquone, isotretinoin, itraconazole, fenofibrate, megestrol acetate, sirolimus, cilostazol, tiagabine, carvedilol, spironolactone, amiodarone)
3. Poor bioavailability requiring higher dose or multiple dosage units per administration (amprenavir, megestrol acetate, ritonavir, eprosartan)
4. Delayed time to achieve efficacy/maximum concentration (diclofenac)
5. Incomplete and unsustained solubilization, particularly in the distal gastrointestinal tract, leading to once-daily dosage form design challenges and dose strength issues (zolpidem, nisoldipine, clarithromycin)

Given the abundance of poorly water-soluble drugs, the pharmaceutical industry faces a continual challenge to overcome these limitations in order to develop innovative, patient friendly products.

Table 1. An Overview of Some Marketed MR Products[2,8]

Drug	Physico-Chemical Nature	IR Dose	MR Product & Dose	MR Formulation	Comments on MR Product
Paroxetine Hydrochloride	pKa: 10.32 log P: 3.457	10 mg, 20 mg, 30 mg; q.d.	Paxil™ CR; 12.5 mg, 25 mg, 37.5 mg; q.d.	Matrix Tablet	25% higher dose compared to IR product daily dose
Isradipine	Solubility in water: 10 mcg/ml	2.5 mg, 5 mg; b.i.d.	DynaCirc® CR; 5 mg, 10 mg; q.d.	Osmotic Release Tablet	Decrease in exposure when given with food; whereas IR product is not effected
Nifedipine	Log P: 2.34 Solubility in water: 1 µg/ml	10 mg & 20 mg; t.i.d.	Procardia® XL; 30 mg, 60 mg, 90 mg; q.d.	Osmotic Release Tablet	Exposure is 86% of IR product
			Adalat® CC; 30 mg, 60 mg, 90 mg; q.d.	Coated Tablet	Increase in exposure when given with food
Ciprofloxacin HCl9	pKa: 6.18 & 8.76 log P: -1.0 Solubility in water: 63 µg/ml Exhibits in vivo absorption window	250 mg, 500 mg; b.i.d.	Proquin™ XR; 500 mg; q.d.	Gastro-Retentive tablets	Bioavailability substantially decreases when administered under fasted condition. Hence, to be taken with food
			Cipro® XR; 500 mg, 1000 mg; q.d.	Bilayer Matrix Tablets	No food effect
Dipyridamole	pKa 6.1 log P: 3.7 Practically insoluble in water	25 mg, 50 mg, 75 mg; q.i.d.	Aggrenox® 200 mg b.i.d.	Extended Release Dipyridamole in Capsule	Decrease in exposure when given with food

Case Study 1. Methylphenidate Hydrochloride[2,8]		
Physico-Chemical Properties	pKa: 8.9; calculated log P: 3.19 Freely soluble in acidic pH and poorly soluble in intestinal pH	
MR Product Brand	**CONCERTA®**	
Dose Comparison	**IR Dose**	**MR Dose**
	5 mg b.i.d. or t.i.d.	18 mg q.d.
	10 mg b.i.d. or t.i.d.	36 mg q.d.
	15 mg b.i.d. or t.i.d.	54 mg q.d.
MR Product Design	Osmotic system with an inner trilayer covered with semi permeable membrane and immediate release over coat.	
Remarks	Higher dose is required for efficient q.d relative to t.i.d. dosing.	

APPROACHES IN DESIGN OF IMMEDIATE-RELEASE (IR) PRODUCTS FOR POORLY WATER-SOLUBLE DRUGS[3]

Most formulation approaches to improve delivery of poorly water-soluble drugs are based on either (1) Techniques to increase the drug dissolution rate and/or achieve transient solubilization, such as particle size reduction, use of high-energy solid forms, or salt forms, or use of co-solvents, or (2) Techniques to achieve a sustained solubilization of the drug, such as complexation, or use of lipid-based delivery systems.

Improvement of Drug Dissolution Rate and/or Transient Solubilization

Particle size reduction has been used to increase the dissolution rate of many poorly water-soluble drugs, but this technique often fails to fully overcome bioavailability limitations and could still result in a high sensitivity to food effects. Recently, the technique of nanosizing (< 0.4 μm) has gained attention with several commercialized products, such as fenofibrate, sirolimus, aprepitant, and megestrol acetate. Like other particle-size reduction techniques, nanosizing vastly improves the dissolution rate, but does not address solubilization, and that could still result in suboptimal oral performance. Therefore, this complex and resource-demanding technique may not be best suited for some poorly water-soluble drugs.

Similarly, high-energy solid forms have been used for numerous drugs, for example chlorpropamide and celecoxib.[4,5] Exploitation of these forms is limited by the possibility of interconversion of polymorphs both during manufacture and storage of the dosage form.

For ionizable drugs, preparation of a more soluble salt form is a common technique to achieve both an increased dissolution rate and a transient increase in solubility. However, this technique, as well as a technique using cosolvents to solubilize can result in uncontrolled precipitation *in vivo* with a corresponding decreased and/or highly variable absorption rate/bioavailability.

Although somewhat helpful to improve drug product performance, these conventional dissolution enhancement/transient *in vivo* solubilization techniques do not improve the transport across the unstirred aqueous boundary layer (ABL) between the bulk intestinal fluid and the intestinal epithelium. For many poorly water-soluble drugs, this transport across the ABL represents the dominant rate-limiting step for drug absorption.[6]

Sustained Solubilization Techniques

Achieving sustained solubilization ensures that the drug will remain solubilized in the gastrointestinal tract for a significant amount of time and could improve the transport rate across the ABL, resulting in the fastest absorption rate.

Complexation using cyclodextrins has been successful for oral delivery of few drugs, such as itraconazole and piroxicam. However, unfavorable binding constants between a given drug and cyclodextrin can necessitate use of a very high amount of cyclodextrin and limit the general utility of this technique.

Case Study 2. Zolpidem Tartarate[2,8]		
Physico-Chemical Properties	pKa: 6.16; calculated log P: 1.88 Very slightly soluble in intestinal pH.	
MR Product Brand	**Ambien® CR**	
Dose Comparison	**IR Dose**	**MR Dose**
	5 mg and 10 mg; q.d.	6.25 mg & 12.5 mg; q.d.
MR Product Design	Coated bilayered tablet, with an immediate release layer and a slow release layer	
Remarks	Higher dose is required for efficacious MR product. Ambien® CR showed decrease in extent and rate of absorption respectively, when given with food, possibly due to increase in gastric pH.	

A few drug products have been developed that offer sustained *in vivo* solubilization with the aid of lipid excipients, such as those for cyclosporine, saquinavir, dutasteride, and amprenavir. Such solubilized systems can eliminate dissolution rate limitations, but the performance is highly dependent on the characteristics of the lipid particles formed upon dilution *in vivo*.

Ideally, lipid-based systems for sustained solubilization should meet the following requirements: (1) spontaneous formation of a stable dispersion with very small particle size in an aqueous environment; (2) high drug solubilization in the dispersed lipid particle; (3) easy partition of the drug from the lipid particle at the site of absorption (enterocyte); (4) maximal drug loading to minimize dosage form size; (5) bioacceptability of the excipients and adequate compatibility for desired shelf life; and (6) ease of manufacture.

Lipocine's Lip'ral™ systems are lipid-based formulations that form micelles upon dilution and are well suited for providing the maximum sustained solubilization *in vivo* and rapid transport across the aqueous boundary layer. The potential advantages of the Lip'ral systems include fastest absorption, lowest effective dose, least variable absorption, and flexibility in administration due to the lack of dependence on physiological factors, including presence or absence of food.

APPROACHES IN DESIGN OF MODIFIED-RELEASE (MR) PRODUCTS FOR POORLY WATER-SOLUBLE DRUGS

In many cases, oral drug delivery products with MR characteristics can result in marked improvements relative to IR products with respect to therapeutic characteristics, pharmacoeconomics, and patient compliance. Modified-release products may also provide prolonged market life for a particular drug. A significant number of the currently marketed products are MR formulations developed subsequent to the original IR products. For example, Cardizem®, an IR product of diltiazem, taken three-times-daily, achieved revenues of $260 million in 1988. A line extension in the form of Cardizem® SR, a twice-daily dosage form, achieved revenues of $400 million in 1989, which remained steady till introduction of Cardizem® CD, a once-daily dosage version. By 1996, sales of Cardizem® CD had soared to almost $900 million.[7] Due to their obvious benefits, MR products will often be the preferred dosage form for optimal therapeutic benefit, and it is expected that ever-increasing numbers of new and existing drugs will be developed as MR products.

Historically, most effort in MR dosage form design has been targeted toward delivery of well-absorbed, water-soluble drugs. Typically, these MR dosage forms were based on monolithic matrix, multiphasic, or osmotic systems or variations thereof.

Some important parameters that need to be critically evaluated in design of a MR oral dosage form include the following:

- the physicochemical properties of the drug;
- the pharmacokinetic characteristics of the drug;
- the physiological factors affecting absorption, such as gastrointestinal transit time, volume, and surface area; dependence on digestive processes; enzymatic metabolism; site-specific absorption; and gastrointestinal pH effects; and
- the desired pharmacokinetic/ therapeutic profile.

Case Study 3. Nisoldipine[2,8]		
Physico-Chemical Properties	Calculated log P of 3.48 Practically insoluble in water	
MR Product Brand	**Sular®**	
Dose Comparison	**IR Dose**	**MR Dose**
	Currently discontinued	10 mg, 20 mg, 30 mg and 40 mg; q.d.
MR Product Design	Extended release (core-coat) tablet formulation with drug present in slow release outer coat and a fast-releasing inner core.	
Remarks	Food with a high fat content increases the C_{max} significantly to about 300%, while total exposure decreased by about 25%. Note: IR product had a less pronounced food effect.	

The particular challenges associated with these parameters when applied to poorly water-soluble drugs have not often been systematically discussed. In many cases, the physicochemical properties of the drug and the sensitivity to physiological factors can make it difficult to obtain the desired absorption profile and can become an issue of major concern obstructing product development.

With more poorly water-soluble drugs in the pipeline of most drug companies and MR emerging as the preferred dosage form, the need for an optimal design and delivery technique has become greater than ever. Conventional MR systems (those without benefit of sustained solubilization throughout the GI tract) have been employed for extended delivery of poorly water-soluble drugs with diverse physicochemical properties. Some examples of such conventional MR products of poorly water-soluble drugs are listed in Table 1, and four detailed case studies are discussed further (Cases 1 through 4).

Despite the use of different controlled-release technologies, these conventional MR products potentially exhibit undesirable attributes suggestive of inadequate solubilization. These observations provide evidence that factors related to drug solubility can become an important rate-determining step for absorption. For example, slow transport across the ABL due to inadequate solubilization may limit the maximum achievable absorption rate leading to poor absorption in the distal gastrointestinal tract. In addition, the significant effects of food on solubilization and gastrointestinal pH may result in significant alterations in the rate or extent of absorption.

Accordingly, in the development of MR dosage forms for poorly water-soluble drugs, the need for sustained and consistent solubilization at the site of absorption has to be considered. To achieve this goal, the requirements include the following:

- Release of both drug and solubilizer should be controlled and synchronized throughout the GI tract to ensure adequate drug solubilization in the lower regions of the digestive tract where the volume of aqueous milieu could be limiting.
- To minimize dosage form size, the solubilizer employed should possess the highest *in vivo* solubilizing capacity for the drug.

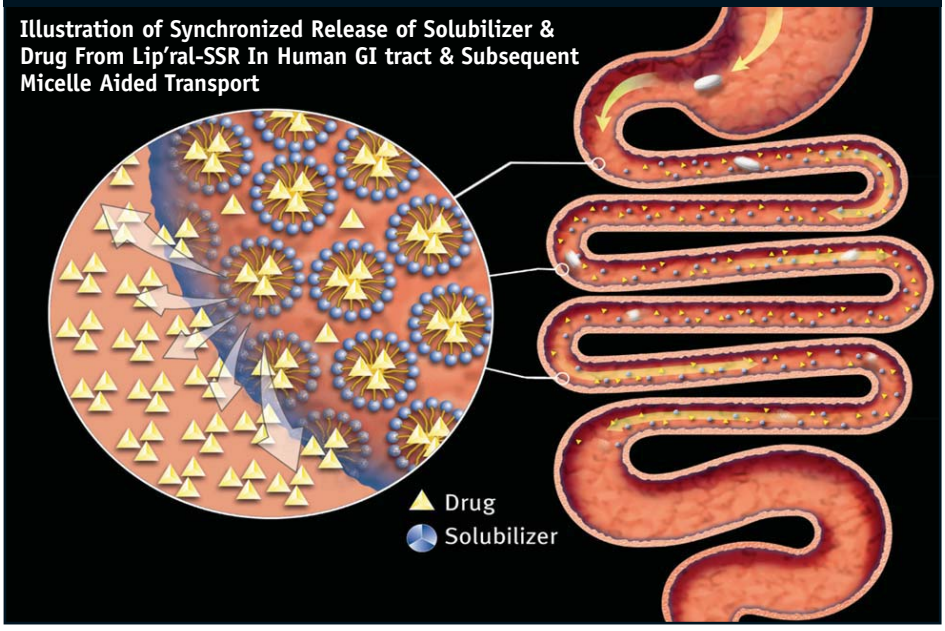
LIP'RAL™-SSR

Lip'ral™-SSR is an MR technology that addresses the aforementioned requirements. Lip'ral-SSR systems can be designed to modulate and synchronize release of a poorly water-soluble drug and Lip'ral solubilizers for delayed, extended, or other forms of targeted delivery in the GI tract. This concept is illustrated in Figure 1. An example of application of Lip'ral-SSR technology to a model poorly water-soluble drug (nonionic, aqueous solubility ~5 µg/ml, calculated log P = 2.6) is shown in Figures 2 and 3.

For drugs with pH-dependent solubility, the Lip'ral-SSR system can control solubilization and release for both pH-independent and pH-dependent target-release profiles. This pH-independent release can be

Case Study 4. Clarithromycin[2,8]		
Physico-Chemical Properties	pKa: 8.76; calculated logP: 2.69 Practically insoluble in water; solubility in general decreases as the pH shifts from acid to neutral suggesting poor solubility in intestinal fluids.	
MR Product Brand	**Biaxin® XL**	
Dose Comparison	**IR Dose**	**MR Dose**
	250 mg, b.i.d.	500 mg q.d.
	500 mg, b.i.d.	1000 mg q.d.
MR Product Design	Film coated extended release tablet	
Remarks	Food effect: C_{max} and AUC decreased by 41% and 30%, respectively, when Biaxin® XL was given in fasting condition. The q.d product is dosed with food. Note: IR dosage form can be taken with or without food.	

FIGURE 1



very useful for poorly water-soluble basic drugs that may show rapid initial absorption due to higher solubility in the gastro-duodenal pH range (1.2 to 5.5) and slow/inadequate absorption at the higher pH range in the lower GI tract. Lip'ral-SSR technology has been successfully applied to a basic drug (pKa ~7.5, intrinsic aqueous solubility ~1 µg/ml, calculated log P = 4.5) requiring solubilization to achieve a more robust and patient friendly product (Figure 4).

SUMMARY

- Sustained drug solubilization in vivo is critical for efficient oral absorption of poorly water-soluble drugs and development of products with superior attributes.
- Conventional MR dosage forms, without benefit of sustained solubilization in vivo, have had limited success when applied to poorly water-soluble drugs.
- Sustained solubilization technologies, such as Lip'ral and Lip'ral™-SSR, could be used to achieve the following:
    - fastest or modulated rates of absorption;
    - effective and consistent bioavailability;
    - once-a-day dosing with lower dose and diverse release profiles;
    - flexibility in administration due to the lack of dependence on physiological factors, including meal contents and timing; and
    - pH-independent product performance for ionizable drugs.
- Lip'ral and Lip'ral-SSR technologies help realize opportunities for optimal delivery of poorly water-soluble drugs that would not otherwise be adequately addressed by conventional technologies.

FIGURE 2

***In Vitro* Synchronized & Controlled Release of the Model Drug & the Solubilizer From a Lip'ral-SSR Formulation**

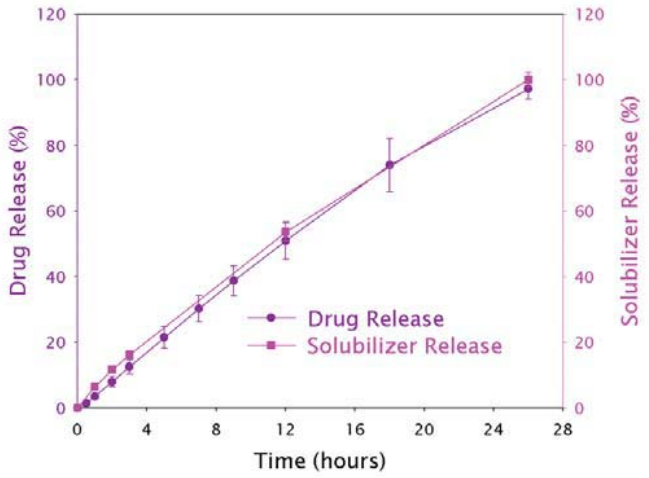


FIGURE 3

Plasma Concentration Profile of the Model Drug From a Lip'ral-SSR System In Humans Compared to the Marketed Immediate-Release Product

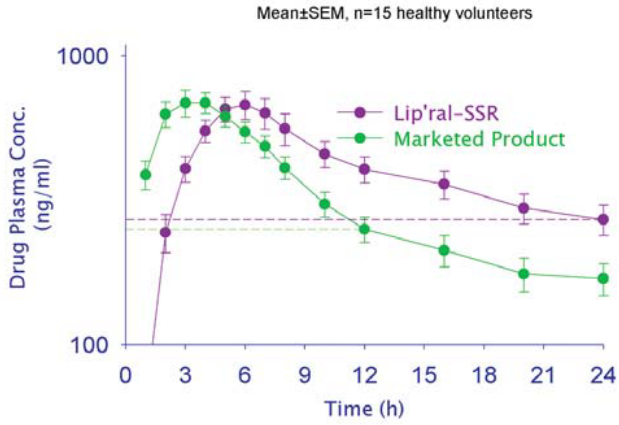
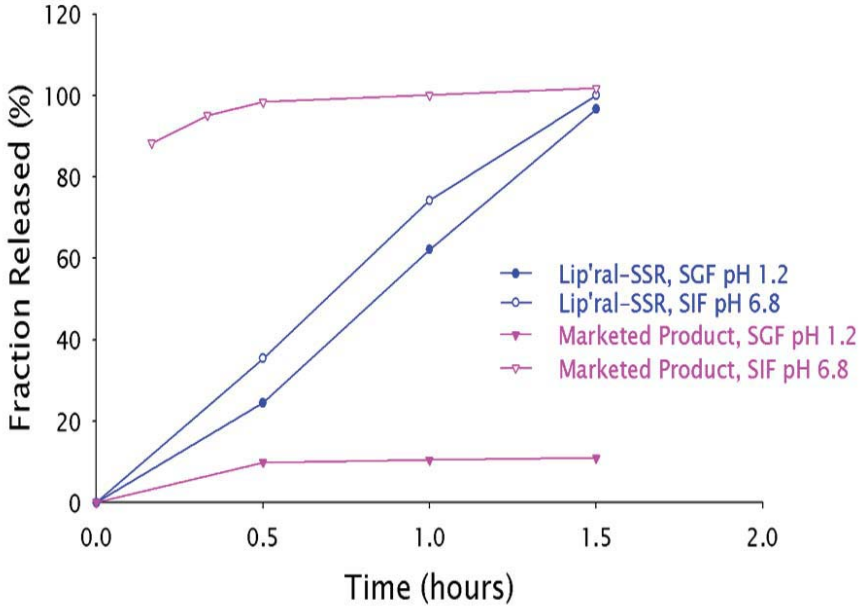


FIGURE 4

***In Vitro* Release Profile From a Lip'ral-SSR Formulation & a Marketed Product In USP Simulated Gastric Fluid (SGF pH 1.2) & Simulated Intestinal Fluid (SIF pH 6.8)**



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BIOGRAPHIES

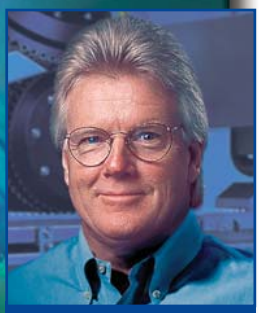
Dr. Chandrashekar Giliyar is a Senior Scientist in the R&D Division of Lipocine Inc. Dr. Giliyar earned his BPharm from Govt. College of Pharmacy (GCP) Bangalore, and his MPharm from M.S. University, Baroda in India (1992). He earned his PhD in Pharmaceutical Sciences from Mangalore University, India (1996), and was a Post-Doctoral Fellow with Dr. William I. Higuchi at the University of Utah. He has worked in the field of formulation and process development for over 10 years in multinational pharmaceutical companies, including SmithKline Beecham/GSK, India. His industrial experience includes development of innovative drug delivery systems as well as development of commercially feasible processes for variety of dosage forms. His research area of interest is novel drug delivery systems for poorly water-soluble drugs and modified-release formulation development. He is a co-inventor in several patent applications and has published articles in peer-reviewed journals.

David T. Fikstad is an Associate Director in the R&D Division of Lipocine Inc. He earned his BS in Chemical Engineering from the University of Utah in 1995. He joined Lipocine in 2000 and has 16 years experience in the field of drug delivery research.

Dr. Shanthakumar T.R. is a Senior Scientist at Lipocine Inc. Dr. Shanthakumar earned his BPharm from Govt. College of Pharmacy, Bangalore, and his MPharm from Mangalore University, India (1993). He earned his PhD in Pharmaceutical Technology from B.V. Patel PERD Centre, M.S. University, Baroda, India (1998) and was a Post-Doctoral fellow with Dr. William I. Higuchi at the University of Utah. He has worked in the field of preformulation, NCE preclinical/clinical formulation development, and drug delivery for more than 12 years. He has almost 7 years experience in multinational companies, including Ranbaxy Laboratories Ltd., and Dr. Reddy's Laboratories Ltd., where he was a key member for filing 6 INDs and several generic products as well getting GLP approval for manufacturing tox-formulations. He has served as a visiting faculty for graduation studies at Hamdard University, New Delhi, India. His current area of research is delivery of insoluble and impermeable drugs, preformulation, salt selection, innovative controlled-release delivery of insoluble drugs as well as clinical manufacturing. He is an invited conference speaker in India, has presented several papers at International Conferences worldwide, and has published articles in peer-reviewed journals and industry reports in the field.

Drug Delivery EXECUTIVE

Safety Syringes, Inc.: Living Up to Its Name Everyday



CHRISTER O. ANDREASSON
Chairman of the Board & Chief Executive Officer
SAFETY SYRINGES, INC.

"Companies, such as Pfizer, AstraZeneca, Johnson & Johnson, Amgen, Bayer, and others, have found Safety Syringes to be a responsive and dependable partner. Numerous pending and issued US and international patents have helped keep us in a leadership position."

Since 1991, Safety Syringes, Inc. (SSI) has specialized in the development of anti-needlestick devices for the healthcare industry. The company's 17 US and International patents, and several additional patents pending, underscore the company's commitment and focus on innovative safety technology. Safety Syringes, headquartered in Carlsbad, California, is now actively developing and marketing its Delivery Systems for prefilled pharmaceutical glass syringes (with over 100 million devices already delivered worldwide), for vaccines, low molecular weight heparins, and other medicines, including many of the newer biotechnology drugs. The company is also aggressively attacking the threat of drug counterfeiting and is the first and only provider of an overt deterrent system, which helps prevent or make evident attempts to adulterate or counterfeit unit-dosed prefilled pharmaceutical presentations. Drug Delivery Technology recently interviewed Christer O. Andreasson, Chairman and CEO of SSI, to discuss his vision on providing clients with the very best and most preferred drug delivery and safety solutions.

Q: When did you get involved in Safety Syringes, Inc. (SSI) and why?

A: After 25 years of working in various management positions for both established and emerging medical technology companies globally, I was fortunate to have established a reputation as someone capable of helping companies navigate change. My experience had taught me what to look for in a company and whether it has the potential to be really great. So in the fall of 1996 when I was asked by the SSI Board of Directors to make an assessment of the company's core technology and intellectual property, I said yes.

At that time, SSI had developed and patented a number of safety products, but none had been particularly successful in the marketplace. I focused on what I believed the market was going to need, not what it was using now. And so, as a result of my initial assessment, my recommendation to the Board was to tailor the technology to the large and rapidly growing prefilled glass syringe market and to abandon dental syringes, disposable hypodermic syringes, and other related safety products. It helped the company realize that a new set of strategic options was not only possible but also necessary. The strategy, in essence, was a reflection of market needs and SSI's ability to adjust to meet those needs.

I was asked to help implement this strategy, and in 1998, was elected Chairman and CEO. It has been a rewarding experience to be a catalyst of major change and to help build a business from scratch based on new needs in the marketplace.

Q: What can you tell us about SSI?

A: I can't tell you much beyond what your readers may know. We need to be guarded a bit due to the competitive nature of our business. But I will say that we have some exciting new products in the pipeline that (even for us) are beyond what the market has been able to predict, let alone produce.

Let me give you a little more background on SSI. We had a very humble beginning and experienced much initial rejection in the early years when calling on the pharmaceutical industry promoting needle safety. But now, and throughout

the past 5 to 6 years, we have been very fortunate to be at the right place at the right time. I prefer to think that "Chance favors the prepared mind," as Louis Pasteur once said.

We were first with a product line addressing needle safety for the prefilled syringe market, initially with our manually activated needle guards. We demonstrated user acceptance of our technology and our products' ease of use. The rapid development and market launch of the UltraSafe® Passive® Delivery System in 2002 (with Pfizer's Fragmin®) helped us position SSI as a market leader.

Q: To what do you attribute the success of SSI?

A: Success in any company or any market is clearly decided by stakeholders and forces in the marketplace. If you can develop and manufacture something that fulfills unmet needs for a price that's fair while satisfying your corporate objectives, then that's a winning formula and that's the formula for SSI.

I do think there are several specific events that helped keep us in the forefront. In the big picture, the *Needlestick Safety and Prevention Act of November 2000* made it all possible. Without this legislation, it certainly would have been a much longer and more difficult journey. In all truthfulness, it may have never happened.

I also believe that we had an advantage in being first to market. Secondly, our overall product performance and corresponding user preference have been very important. Additionally, our product platform development has been very timely and has accurately met an evolving array of different market needs. And finally, I'd say our sole focus on drug delivery systems for the prefilled syringe market has proven to be an excellent position for SSI in creating some strong corporate alliances.

Q: Your customer list contains most of the top pharmaceutical companies in the world — why did they choose SSI over other technical solutions?

A: We're known by the companies we keep. Pharmaceutical companies are very careful in selecting their partners, and SSI is keenly aware that those relationships can be significant for the long-term. But it takes a real commitment on our part in dealing with the problems these companies must address.

That said, I would like to think that product performance and user preference play the most important roles. But also our time-to-market performance, customer support, and responsiveness are important factors in our partners' decisions. I think another reason we have been selected is the availability of assembly automation systems from leading machine builders. This allows us to facilitate streamlined integration into secondary packaging lines, a clear advantage in my view.

Q: You recently gave a talk about the ever-increasing global concern for counterfeit drugs. How has SSI been able to take the lead in combating counterfeit issues?

A: Counterfeit drugs are a BIG global business and as such, have attracted interest from organized crime. The number of investigations by the FDA has tripled throughout the past few years. We are actively attacking the threat of drug counterfeiting. We are the first and only provider of an overt deterrent system, which helps prevent or make evident attempts to adulterate or counterfeit unit-dose, prefilled pharmaceutical presentations. It's a tamper-evident version of the UltraSafe Passive Delivery System — an overt deterrent — which makes it more difficult for counterfeiters to copy brand name drugs packaged in the system. It provides another layer of protection and is at the unit-of-use level, which is what the FDA recommends for the counterfeiting solution.

I think these counterfeiting issues (especially when they are backed by organized crime, which has lots of resources) will be with us for some time. SSI has made a good first effort; but believe me, this will be a long-term battle.

Q: You have established partnerships with leading companies for assembly automation, secondary packaging, and product labeling. Why did you do this and how has that helped in achieving your success?

A: It's been our SOP to partner for the best interest of the market and the success of the product development team. I should point out, however, that we do not charge off after every new opportunity. I believe that we have a very good gauge on what is needed now and what will be needed in the future. We're selective; but once we select, we are committed.

The decision to partner for assembly automation and product packaging and labeling was made very early, and I believe that the success we have had suggests that it was the right thing to do. It took a bit of convincing initially and certain investments on our part to make it happen. The biggest benefit to the pharmaceutical industry has been the shortened time to market as assembly automation and secondary packaging machines were available for rapid and smooth integration. As a matter of fact, we developed an in-house assembly system very early on. This was before we realized that pharmaceutical companies had preferences for certain machine builders. Some had dealt with specific suppliers for the past 15 to 20 years.

The product labeling relationship we have established with Schreiner has already benefited both parties, and some very interesting opportunities are presently on the table.

Q: Your partnership with Ypsomed and the joint development of an auto-injector for use with your UltraSafe Passive Delivery System has gained a lot of attention lately. Why was this partnership an important step to take?

A: Whenever you can partner with a market leader, you're in good company. That's why our partnership with Ypsomed makes tremendous sense; it gives us entry to the self-administration market, which already is large and growing fast. Market research, which we have recently completed jointly with Ypsomed, shows an overwhelming preference — almost 90% for the combined product when compared to a conventional syringe alone or a conventional syringe in combination with an auto-injector, which is what is being used today for several self-administrated drugs. We believe this will be a valuable partnership between two market leaders, each successful in its own field.

Q: What is next for SSI?

A: Good question. I don't know the exact answer, but I know the answer lies in the market, the needs of the consumer, and our ability to respond. Albert Einstein observed, "The significant problems we face cannot be solved at the same level of thinking we were at when we created them." We totally agree. And since 1999, SSI has specialized in the development of anti-needlestick devices for the healthcare industry that have led the way.

To that end, we are busy expanding our manufacturing and assembly capabilities to meet forecasted customer needs. We are working diligently on significant product launches in two new and exciting drug segments — vaccines and generic injectables. Simultaneously, we are in the late stages of two additional product indications, one with a leading biotech company and another with a global top-ten pharmaceutical company. Furthermore, we recently entered into a development agreement for a custom product based on the patented UltraSafe Passive Delivery System for another top-ten pharmaceutical company. But this is not all. In a new partnership, soon to be announced, we will enter yet another large market with unfulfilled needs — stay tuned for more!

Q: What is SSI's biggest challenge and opportunity today?

A: To stay focused and not to stray from our core competency. That focus has served us well with innovative safety technology that consistently helps us bring new products to market while assisting our partners in solving a myriad of application challenges for the prefilled syringe market.

Companies, such as Pfizer, AstraZeneca, Johnson & Johnson, Amgen, Bayer, and others, have found Safety Syringes to be a responsive and dependable partner. Numerous pending and issued US and international patents have helped keep us in a leadership position.

Our UltraSafe product platform has delivered more than 100 million devices worldwide, while our partner count has increased steadily and will soon be providing over 20 different drug products worldwide.

So what's the challenge? To continue to innovate and build on our product platform. To stay ahead of the competition by offering pharma partners less risk and the shortest time to market. To provide more variety and better choices with the best possible customer service. And to continue to earn top rankings in user preference studies with products that are intuitive to use and that require little or no training. Last but not least, we must maintain our unparalleled quality record.

Q: As an industry leader, what do you think the marketplace for your products will look like in five years?

A: Five years is a long time and products and markets change. I think our philosophy and innovative mindset keeps us alert and in the forefront, so I may not know exactly what we'll be selling in 5 years, but I know that whatever we're making, it will be there because the market wants it. And hopefully, we will continue to make better products than anyone else.

Still, predicting the future is not easy. I believe that the market will look both different and the same, if that makes any sense at all. Let me try to explain what I mean. On one hand, it will be different because it will be much more developed and most likely fully converted to safety. At the same time, I think the drivers and many of the challenges will be the same. Decisions by pharmaceutical companies to convert to safety systems will continue to be based on fundamentally sound business economics, either to gain a competitive advantage and hence gain market share, or to prevent or slow down market share erosion.

I also believe there will be anti-needlestick legislation in most European countries in 5 years, but I do not think this legislation will drive any significant shift in the market. I am, of course, hopeful that throughout this we will be able to remain a market leader and an industry benchmark for innovation. ♦

Drug Delivery Showcase

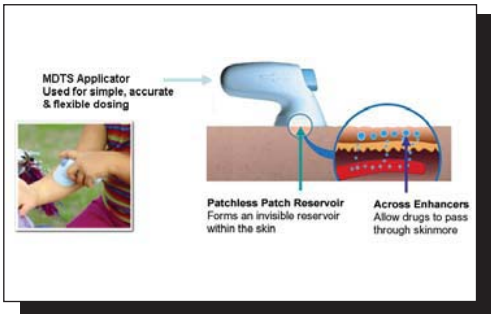
Transdermal & Film Delivery

Aveva Drug Delivery Systems owns proprietary transdermal formulation and manufacturing technologies, which focus on elegant "matrix" patch designs allowing for the incorporation of drugs into adhesives that attach the patch to the skin. The broad range in technology and experience includes solubilized matrix, crystal dispersions, multi- or single-layer systems, membrane-controlled systems, specialized proprietary adhesives, and packaging technologies. These technologies can be optimized to suit particular drug characteristics and product needs, and are rapidly developed from feasibility stage through clinical and commercial production stages. The company provides vertical integration of adhesive, film coating, and transdermal formulation technology to produce the most efficient and cost-effective products, and is applying its transdermal technology to proprietary and generic drugs. For more information, visit **Aveva Drug Delivery Systems** at **www.avevadds.com**.

Prefilled Needle-Free Delivery System

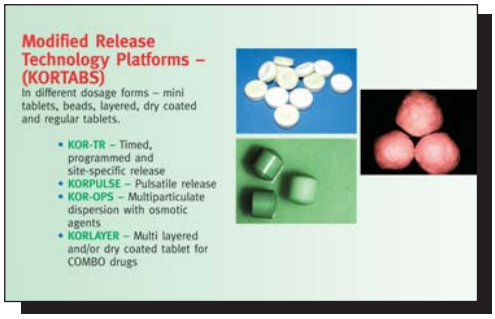
The Mini-Ject represents the next generation in needle-free injection systems by combining the features of accuracy, reliability, variety of prefilled options, comfortable administration, and full disposability, all within a patient friendly easy-to-use design. The Mini-Ject can deliver a wide range of drugs, ranging from small molecules to large proteins, fragile antibodies, and vaccines. Delivery can be targeted to intradermal, subcutaneous, or intramuscular, depending on the clinical need. No other single-use needle-free delivery technology provides the same level of performance as the Mini-Ject technology with the ability to target specific tissue layers over such a broad range of drug volumes (0.1 mL to 1.3 mL) and viscosities. For more information, contact **BioValve** at (508) 366-2300 or visit **www.biovalve.com.**

Transdermal Delivery



The MDTS® is a small and easy-to-use drug delivery system containing an existing therapeutic drug and ACROSS® penetration enhancers, which are small, lipid-like compounds that allow drugs to pass through the skin. ACROSS penetration enhancers are GRAS due to their long-term and extensive use on humans. MDTS provides a simple way of applying a preset dose of a drug to the skin. It is placed gently against the skin and depressed releasing a light spray, which quickly dries on the skin. The ACROSS enhancers then allow drugs to pass through the top layers of the skin. A once-a-day application typically delivers consistent amounts through the skin to the blood stream. For more information visit **Acrux** at **www.acrux.com**.

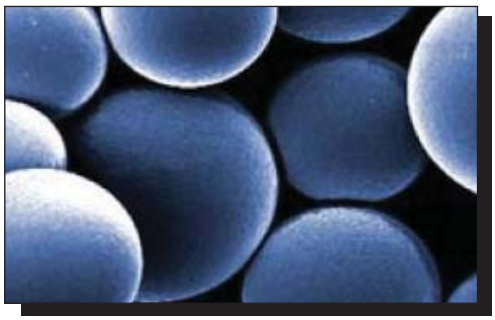
Solid Oral Delivery Systems



KORTABS technology is the combination of the mechanism of controlled release, based on the formation of hydrophilic matrices using medium and long-chain polymers, with the advantage of multiparticulate dosage forms. This combination allows the formulation of products based on APIs with a wide range of solubility profiles, with virtually any kind of dissolution pattern. As the total dose is divided in to subunits, it is possible to obtain, with the same formulation, different dosage strengths. Capsules formulated with KORTABS are mono-dispersed systems; each possesses exactly the same biopharmaceutical behavior of others. Different kinetics of dissolution, and in vivo absorption, can be designed to obtain the optimal input of the drug into the body, for the most effective therapeutic and safety profile. Fore more information, contact **Capricorn Pharma** at 301-696-1452 or visit **www.capricornpharma.com**.

Drug Delivery Showcase

Controlled Release

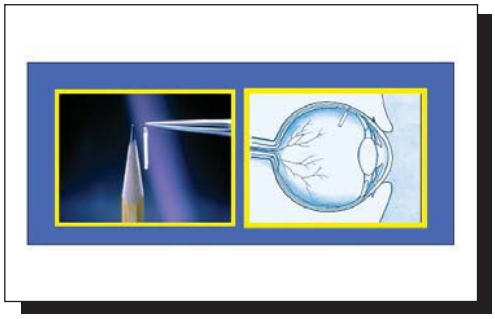


OctoPlus is a product-oriented drug delivery company that focuses on the development of innovative drug delivery systems. OctoPlus' key proprietary technologies, OctoDEXTM, PolyActiveTM, and SynBiosysTM, enable the development of tailor-made controlled-release formulations for all classes of injectable drug compounds. Using its controlled- release drug delivery technologies, OctoPlus can design products that are more patient friendly and potentially safer and more efficacious. OctoPlus' partnering strategy includes offering its drug delivery technologies for licensing to third parties on a product-by-product basis. The company has entered into several product partnerships with third parties to co-develop sustained-release formulations. For more information, contact **OctoPlus** at +31-71-5244044 or visit **www.octoplus.nl**.

Manufacturing Solutions

Since 1949, Remmele Engineering has designed and built custom manufacturing equipment for installation worldwide. The company is an innovative, strategic thought partner for leading suppliers in the drug delivery industry. Remmele operates under an ISO 9001:2000-certified quality system and provides manufacturing solutions from proof-of-concept through commercial manufacturing. Its world-class facility is equipped to streamline critical manufacturing while reducing risk in even the most complex applications. Utilizing leading-edge applied technologies for web processing, discrete assembly, and packaging & filling, the company focuses all of its energy and experience on the singular task of meeting customer needs. Its ability to identify unique customer needs, provide custom solutions on time and superior results every time is unrivaled. For more information, visit **Remmele Engineering** at **www.remmeleautomation.com**.

Intraocular Implant



ECT Technology consists of implantable devices containing cells encapsulated within a semi-permeable membrane, isolating them from the local environment and minimizing immune rejection, but allowing therapeutic agents produced by the cells to diffuse through the membrane. ECT is also a product-based concept, supplied as a ready-to-use device with the added advantage that the product can be withdrawn if required. The feasibility of ECT implantable devices has already been demonstrated in human clinical trials to treat chronic pain and amylotropic lateral sclerosis, and is now being applied in the eye. Because cells can be modified genetically to secrete almost any protein, ECT is an extremely powerful technology platform, strongly and broadly patented, with the potential of generating a broad product pipeline in multiple therapeutic areas. For more information, visit **Neurotech** at **www.neurotech.fr**.

Technologies & Services

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Drug Delivery EXECUTIVE

TransPharma Medical: Unmatched Applications in Transdermal Technology

DR. DAPHNA HEFFETZ
Chief Executive Officer
TRANSPHARMA MEDICAL

"As the company's core technology evolved into a robust and well anchored transdermal drug delivery product, we recognized that the skills and the knowledge that had developed and accumulated within the company throughout the years now enabled the possibility for independent development of its own product pipeline."

TransPharma Medical is a biopharmaceutical company focused on the development and commercialization of pharmaceutical products utilizing RF MicroChannel technology, the company's proprietary active transdermal drug delivery technology, developed to address the limitations of current transdermal delivery. Drug Delivery Technology recently interviewed Dr. Daphna Heffetz, TransPharma Medical's Chief Executive Officer, to learn more about the company and how its RF MicroChannel technology and patch formulation capabilities come together to offer a painless, needle-free platform that improves the delivery of a wide variety of small molecules, proteins, vaccines, and other biotechnological macromolecules.

Q: Please describe your technology and what makes it unique

A: TransPharma's technology combines the application of RF energy to the skin with unique drug formulations to deliver small molecule and protein therapeutics transdermally in a highly consistent and reproducible manner. Our development group has adapted RF technology in the form of a small, handheld device that, when pressed lightly on the skin, quickly and painlessly creates microscopic channels through the stratum corneum. These channels, which we call RF Microchannels, expand the portfolio of drugs that can be delivered transdermally and have enabled TransPharma to demonstrate, for the first time, the delivery of therapeutically meaningful levels of biologics to the systemic circulation.

By harnessing the unique attributes of RF energy, TransPharma's technology is unmatched in its ability to precisely define the depth, density, and diameter of the RF Microchannels and, ultimately, the delivery profile of the drug to the target. And, because our device technology stands alone from the drug, it can be combined with existing patch or topical drug formulations as well as with TransPharma's proprietary dry protein patch formulations. These unique features of TransPharma's technology provides for its wide applicability in the areas of systemic drug delivery, both of small molecules and biologics, topical drug administration, and vaccination. We are aware of no other transdermal technology with such wide applicability.

Q: Can you discuss TransPharma Medical's background and how it evolved from simply licensing its technology to big pharmaceutical companies to develop its own products?

A: In its early years, TransPharma Medical was focused on the strengths of its core transdermal drug delivery platform, and strategically positioned the technology to be incorporated in products collaboratively developed with pharmaceutical companies. As the company's core technology evolved into a robust and well anchored

transdermal drug delivery product, we recognized that the skills and the knowledge that had developed and accumulated within the company throughout the years, now enabled the possibility for independent development of its own product pipeline. Through this mix of partnered and proprietary product development, we believe we are capitalizing both on the promise of the technology and growing capabilities of the company.

Q: How proven is the ViaDerm™ technology? What types of products are the most likely candidates to benefit

A: The ViaDerm device is TransPharma's first commercial prototype employing the RF Microchannel technology. As such, TransPharma's RF MicroChannel technology has been validated in a large number of animal models and in four human clinical studies. Validation studies have demonstrated the wide applicability of the technology with small molecules, peptides, and proteins (regardless of size), vaccines, and polynucleic acids. There are many types of drugs that could benefit from TransPharma's technology. TransPharma is focused on those drugs for which our technology will provide clear benefits over the existing therapy. Such benefits could be in the form of improving safety and compliance through the use of a drug patch or enhancing efficacy with the use of sustained-release patch formulations, for example. There are also product candidates, whose ultimate therapeutic use can be enabled with TransPharma's technology, including transcutaneous vaccines, topical peptide or protein-based drugs for dermatologic applications, and product candidates in the area of iRNA therapies.

Q: What is attractive about ViaDerm?

A: The ViaDerm and the additional device designs under development at TransPharma are handheld devices which are pain-free, low cost, extremely portable, and require only a few seconds of simple operation. They are designed to be reusable for more than 1000 applications and are intended for home use by the patient. The underlying device technology makes it applicable for use with a wide variety of patch technologies and topical drug formulations.

From a medical and regulatory perspective, the ViaDerm and future device products are designed to create RF Microchannels consistently and reproducibly within and between patient populations. For the physician, this means patients will benefit from optimal drug delivery within a desired therapeutic range. For the regulator, this means that our technology will allow for minimal variations in drug plasma levels compared to the reference drug. This is also an important consideration in the pursuit of a 505(b)(2) regulatory pathway for approval.

Q: When will ViaDerm be available on the market

A: TransPharma is pursuing its pipeline development along two parallel paths. The first path is through partnerships, and the second path is through independent development. Through this approach, TransPharma can fully exploit the wide applicability of our technology and benefit from early, mid-, and long-term revenue opportunities. In this respect, we expect some of our dermatologic and topical products to enter the market as early as 2007.

Q: Is TransPharma involved in partnering with other pharmaceutical companies?

A: Following its partnership development path, in late 2004, TransPharma entered into a long-term comprehensive development and commercialization agreement with Teva Pharmaceuticals Ltd. Other potential partnerships are underway but are currently in early stages and for strategic reasons may not be disclosed yet.

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

A: TransPharma's long-term goal is to build a profitable and sustainable business for our technology across multiple products and markets. We believe this is in the best interest of our shareholders and have assembled a top-rate management team to execute on this objective. We recognize the inherent risk in introducing any novel drug delivery technology to the market. We seek to mitigate this risk through a thoughtful and methodical approach to gaining credibility for our approach with physicians as soon as possible while gaining access to near-term sources of revenue.

TransPharma Medical is at a crossroad as we move from a drug delivery platform company to a product-focused company. This time has its own unique set of challenges, not the least of which is the sourcing of capital for operations. However, we are confident that our technology and business model represent a very attractive investment thesis. ♦

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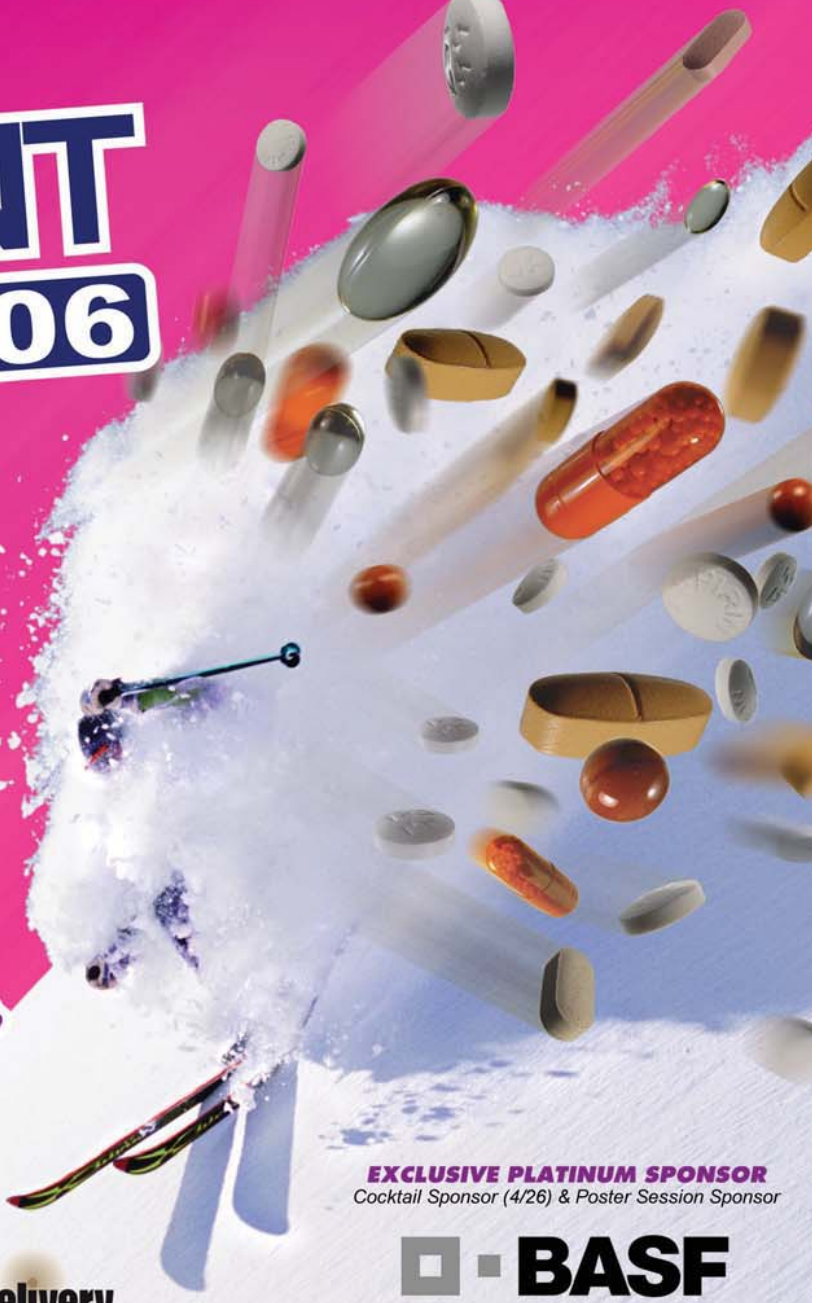

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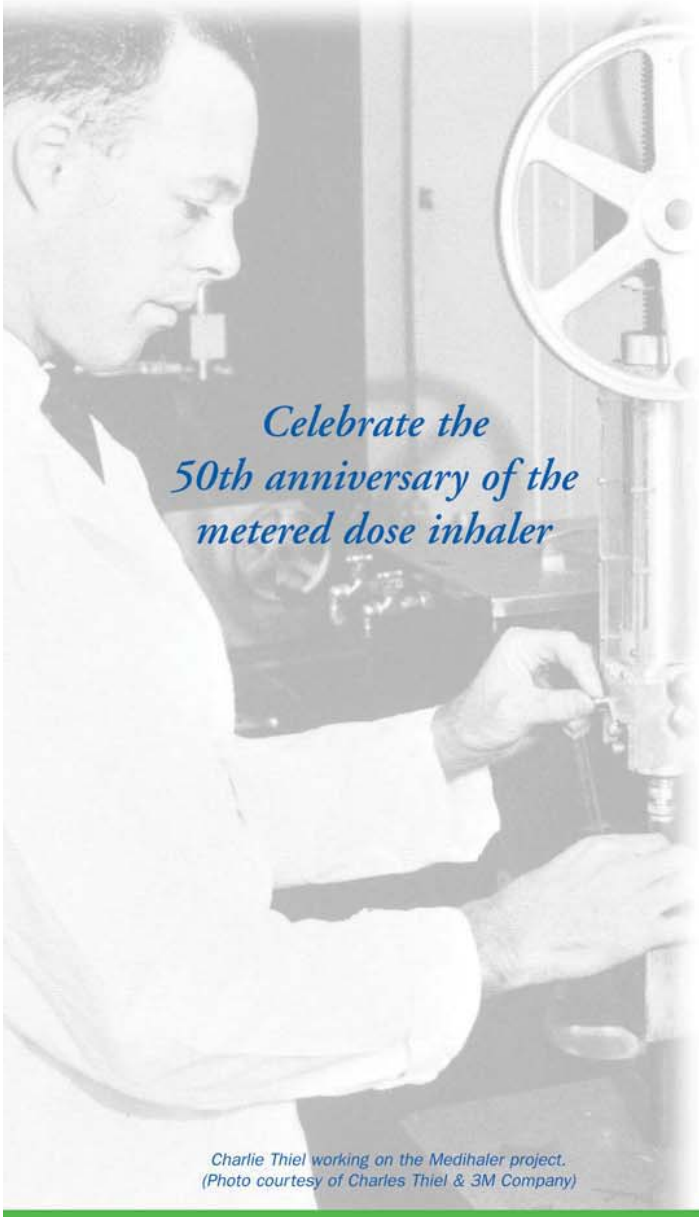

Charlie Thiel working on the Medihaler project.
(Photo courtesy of Charles Thiel & 3M Company)

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Consistent Flexibility

By: John A. Bermingham

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.

I once had a boss who I will call Fred (not his real name). Fred was very inconsistent in his personality and management style from day to day. Some days were very very good, and some days were very very bad. Fred was carrying a lot of baggage around and it really affected him.

It was so bad that we named his alter ego Frank. Fred was good. Frank was bad.

So when Fred arrived at the office each morning, the management team would check in with each other to see if it was Fred or Frank that had arrived at the office that morning.

If Fred was in town, then we knew that we were going to have a good day. If Frank was in town, then it was a very different story. Sometimes Fred would arrive in the morning only to have Frank with us in the afternoon.

This is not what I mean by consistent flexibility. I think the Fred/Frank issue might be better described as inconsistent flexibility. Following the Fred/Frank experience, I developed a management theory called Consistent Flexibility.

This means that you have to have a degree of flexibility in your management style that remains consistent so that you don't drive the people in your company out of their minds. Let me explain.

People who work with me learn that I have a degree of consistent flexibility. Not wishy washy but not totally locked into the company Policy and Procedure manual 100% of the time. Sometimes you have to close the manual and do what makes sense. People know that if they bring a logical substantiated reason for being flexible on a policy or procedure, then I will look seriously at their proposal. Conversely, I am consistent in my position of rejecting a proposal that is not well thought out or it becomes apparent that the person is "shooting from the hip." That really fries me.

People who work with me learn quickly that I am a morning person. Thus, complex, controversial, or critical issues that may require some flexibility on a company policy are best brought to me early in the morning, not late in the afternoon. Fridays are the best day of the week to meet with me. So Friday morning is absolutely the best time to meet with me when flexibility is required. I think that this stems from my school days when Friday was absolutely the best day of the school week.

People learn that I am a visual type of person, so complex issues are best understood if you bring the issue in a Power Point format. If the presentation is strictly verbal, then it takes much longer for me to understand it, if at all. And that makes me cranky. So Friday morning should be prime time.

People understand this so well that I eventually had to put one of those take-a-number machines outside my office due to the line up of people on Friday mornings, Power Point presentations in hand. People also learn how far to push me as I try to remain consistent in that area of flexibility on policy or procedure.

So you might consider a degree of consistent flexibility in your management style so that people know that you will listen carefully and react in a consistently flexible manner to their ideas and proposals. Oh yeah. After 25 years of marriage, my wife has also learned well how to manage within my consistent flexibility. She seems to always get what she wants. How does she do that? ♦

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