Drug Delivery Technology®

June 2006 Vol 6 No 6

Identifying Parameters of Value

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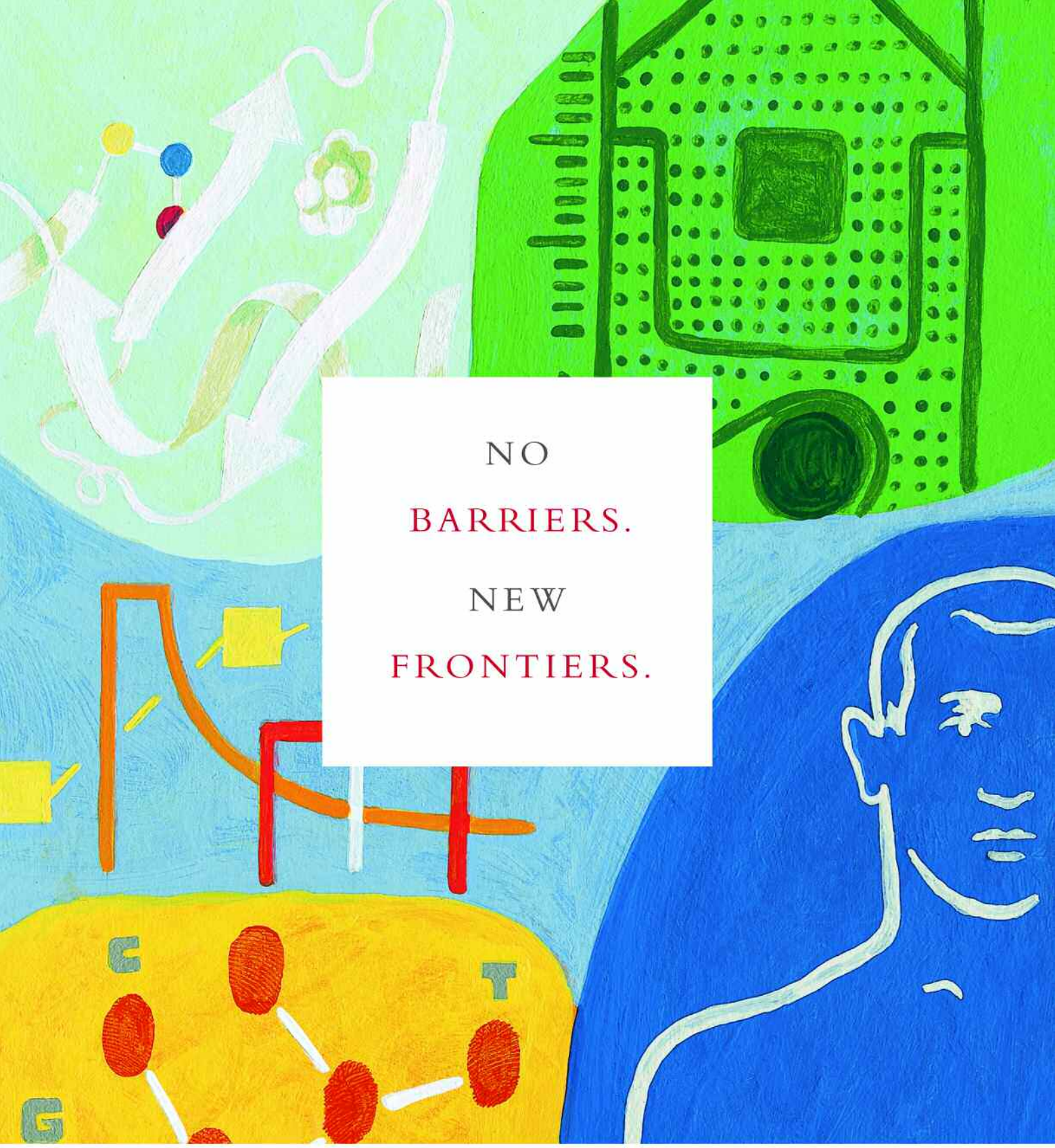

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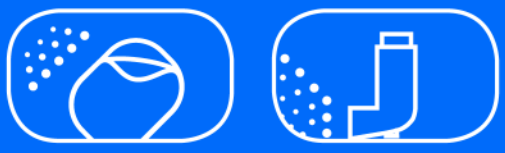

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Corporate/Editorial Office
219 Changebridge Road, Montville, NJ 07045
Tel: (973)299-1200
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www.drugdeliverytech.com

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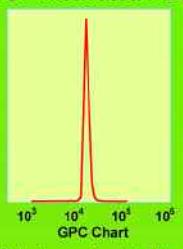

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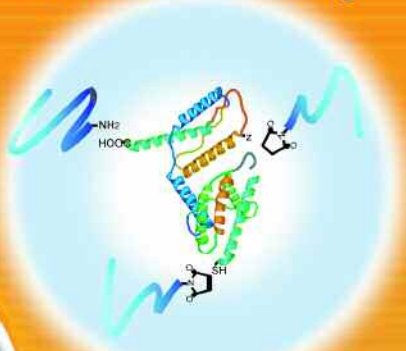

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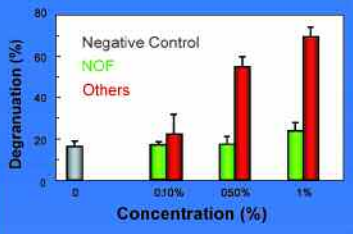

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DDS Development Department
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http://www.nof.co.jp/dds/ E-mail: ddsinfo@nof.co.jp
Tel:+81-3-5424-6741 Fax:+81-3-5424-6769

NOF America Corporation
11 Martine Avenue, Suite 1170, White Plains, NY 10606, USA
TEL: +1-914-681-9790 FAX: +1-914-681-9791
E-mail: info@nofamerica.com

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

Identifying Parameters of Value

"Is one pipeline really that much better than another? Is it better to have two potential $500-million products at Phase I than one $100-million product at Phase III? It's a tough call, and one that's worth looking at if the hard numbers don't reveal anything."

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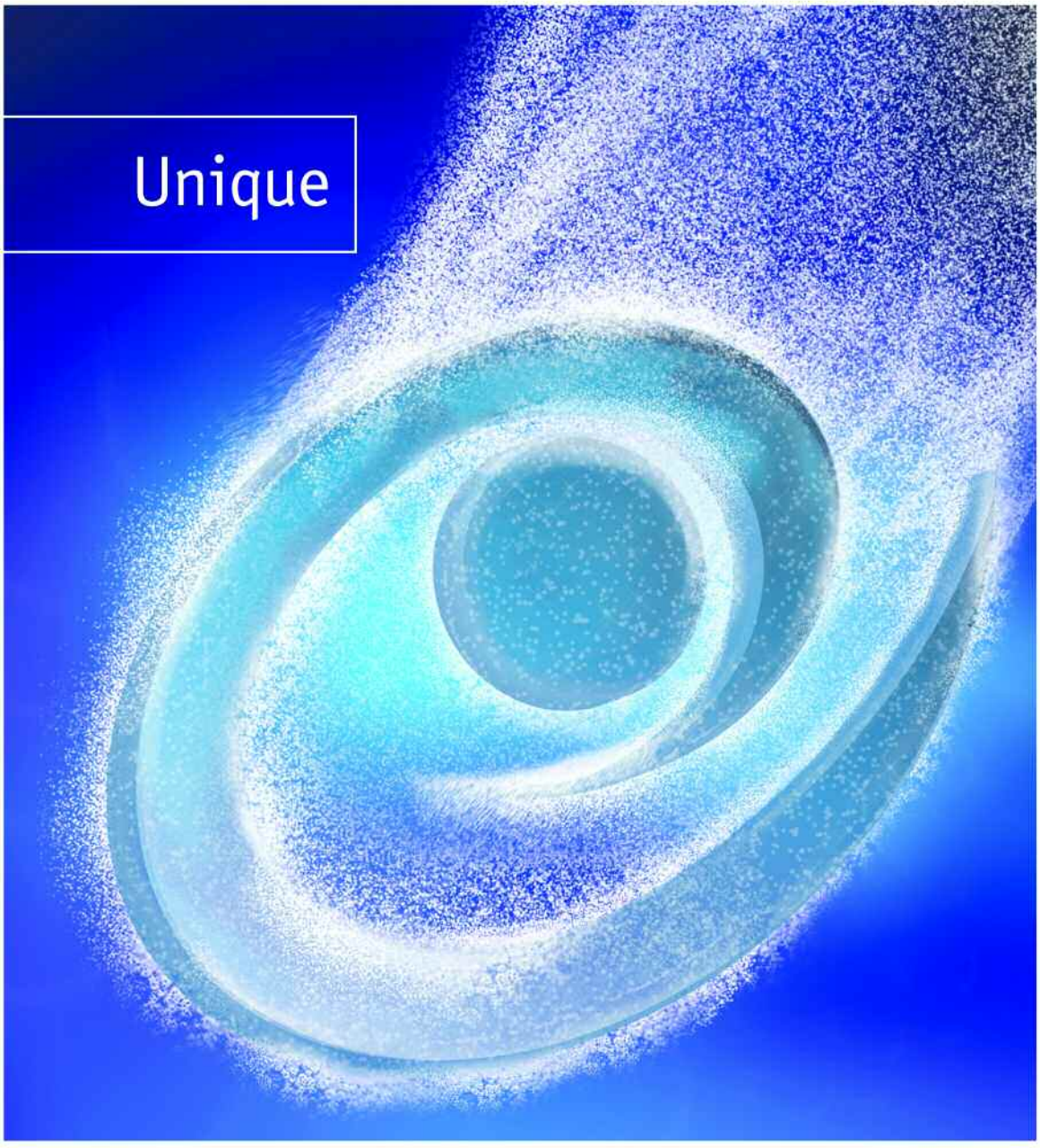

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Chronotherapeutic Challenges

"It is obvious that chronotherapeutics represent a significant challenge to the drug delivery sector. The dosage forms have to cope not only with the significant physiological variations they will encounter, but they will have to precisely deliver their payload of drug to a specific time window."

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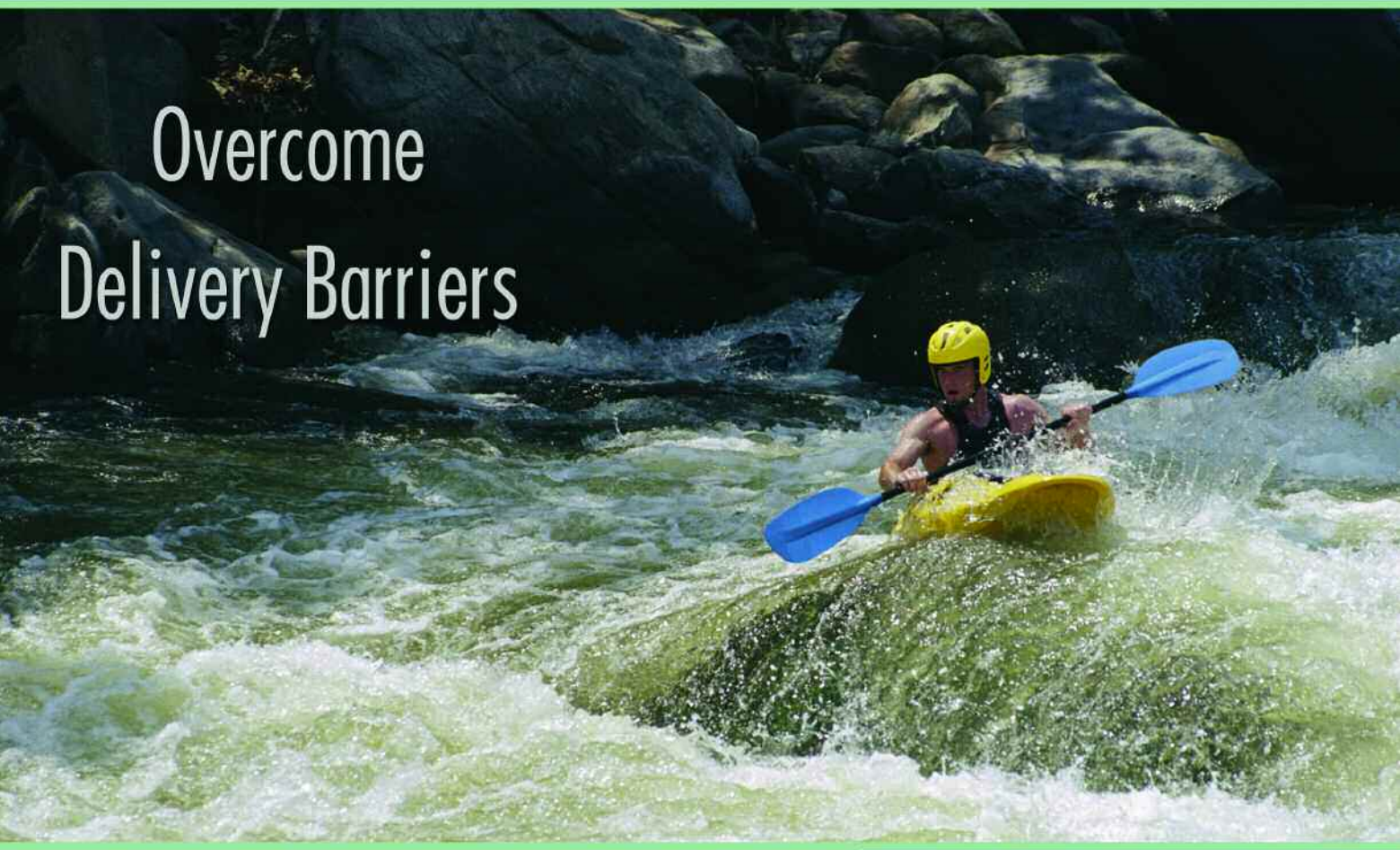

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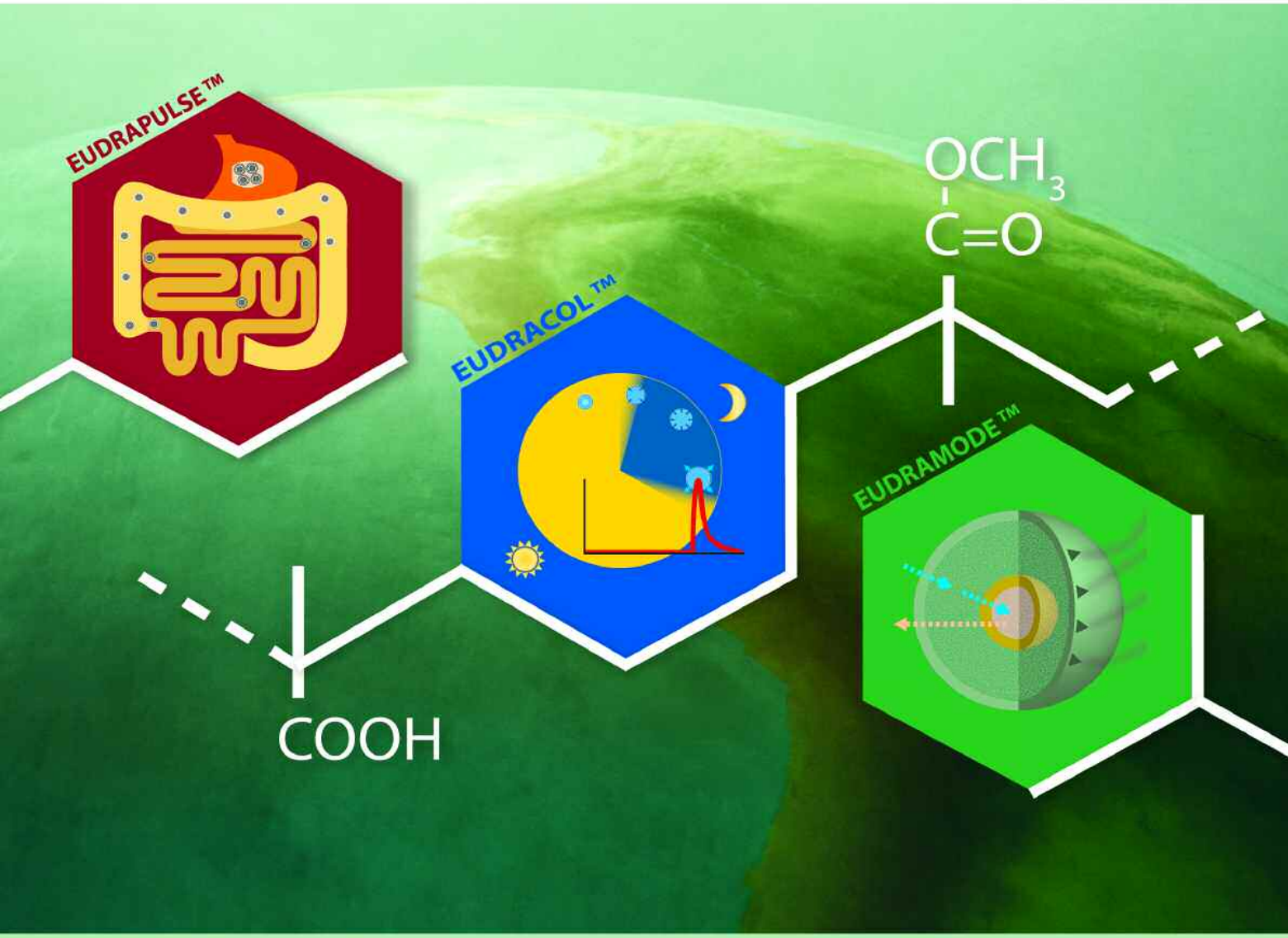

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Market News and Trends

Kos Pharmaceuticals & SkyePharma Sign Exclusive License Agreement for Flutiform in the US; Includes $25-Million Licensing Payment

Kos Pharmaceuticals & SkyePharma Sign Exclusive License Agreement for Flutiform in the US; Includes $25-Million Licensing Payment
Kos Life Sciences, Inc., a subsidiary of Kos Pharmaceuticals, Inc., and Jagotec AG, a subsidiary of SkyePharma PLC recently announced the signing of an exclusive agreement for the marketing and distribution in the US of SkyePharma's product, Flutiform. Flutiform is a formoterol and fluticasone fixed-dose combination in a HydroFluoroAlkane metered dose inhaler. The strategic partnership includes an upfront licensing payment of $25 million. If all regulatory and sales milestones are met, SkyePharma could receive up to an additional $140 million in payments, plus mid-teens sales royalties.

Patients with asthma are normally treated with two types of therapy: an anti-inflammatory drug that addresses the underlying cause of the condition, and a bronchodilator that opens the airways, relieving the symptoms and allowing patients to breathe normally. The older short-acting bronchodilators, although used for treating acute asthma symptoms, have now largely been displaced by long-acting bronchodilators that provide symptom relief for 12 hours (particularly valuable overnight) on a chronic basis and for prevention. Asthma drugs can be taken orally but most are inhaled, with the active drug delivered to the inner surface of the lung by means of an inhaler device, either a metered-dose aerosol inhaler or a breath-actuated dry powder inhaler. The US market for asthma drugs exceeded $10 billion in 2005. The fastest-growing segment of this market is with fixed combination treatments, which combine a long-acting bronchodilator with an inhaled steroid in a single delivery device. Combinations are not only more convenient for patients than carrying two separate inhalers, but also have been shown to optimize the efficacy of the individual agents.

"We are very pleased with SkyePharma's clinical development of Flutiform for the asthma indication and are excited about this commercial opportunity in a very large and expanding market segment," commented Adrian Adams, President and Chief Executive Officer of Kos Pharmaceuticals, Inc. "This strategic partnership should broaden our presence in the respiratory area, and provides a high potential partner product for Azmacort, our inhaled corticosteroid therapy. Our partnership with SkyePharma is another excellent example of Kos' expanded business model that includes measured and therapeutically aligned investments to fortify our R&D pipeline through corporate development and scientific in-licensing activities. In addition, it provides an opportunity to diversify our product portfolio by creating yet another potentially significant revenue-generating opportunity anticipated in 2009, further reinforcing our objective to launch at least two products a year through the end of the decade, beginning in 2007."

SkyePharma's Chief Executive, Frank Condella, added, "We are delighted to announce this partnership with Kos for our major pipeline product Flutiform. Kos has a tremendous track record of successful marketing with its cholesterol product, Niaspan. Over the past 5 years, sales of Niaspan have increased at a compound annual growth rate of over 50%, helping Kos to become the fastest growing pharmaceutical company in the US, and the sixth fastest growing of all US companies in 2005. Kos is also active in the respiratory market with its recently acquired inhaled steroid product, Azmacort. Kos currently has a sales force of 750 concentrated in the cardiovascular and respiratory markets, and plans to increase to over 1000 representatives by the time that Flutiform is launched. We believe Kos brings a therapeutically focused marketing approach that will optimize the commercial potential of Flutiform in the key US market."

SkyePharma will retain the commercial rights to Flutiform outside the US and Canada and continues to be responsible for Flutiform's Phase III clinical trials and regulatory approval in the US. SkyePharma will also be responsible for the supply of the product. Kos' responsibilities include the commercialization of Flutiform, the potential clinical development of COPD and Pediatric Asthma indications, and all Phase IIIb and Phase IV studies.

SkyePharma's product Flutiform consists of a unique fixed-dose combination of the long-acting bronchodilator formoterol with the inhaled steroid fluticasone in a proprietary non-CFC metered-dose aerosol inhaler with a dose counter. Formoterol provides 12 hours of bronchodilation and has a rapid onset of action (1 to 3 minutes). By contrast salmeterol, the bronchodilator used in GlaxoSmithKline's Advair/Seretide, also provides 12 hours of bronchodilation, but needs up to 30 minutes after inhalation to take effect. The inhaled steroid fluticasone (a component of Advair/Seretide) has low systemic absorption and is perceived to have a better safety and efficacy profile than budesonide, the steroid used in AstraZeneca's Symbicort, and is the physician-preferred inhaled steroid in the US. The proprietary SkyeDry formulation technology employed in Flutiform, designed to stabilize the active components and thereby ensure a reproducible dose even after prolonged storage, provides patent protection to 2019. The product will be available in two dose combinations with each dose delivering 10 micrograms of formoterol with either 100 or 250 micrograms of fluticasone.

Kos Pharmaceuticals, Inc., is a fully integrated specialty pharmaceutical company engaged in developing, commercializing, manufacturing, and marketing proprietary prescription products for the treatment of chronic diseases with a particular focus on the cardiovascular, metabolic, and respiratory disease areas. The company's principal product development strategy is to reformulate existing pharmaceutical products with large market potential to improve safety, efficacy, and patient compliance. Kos' strategy also includes making measured investments in new chemical entity research through in-house and sponsored research, scientific in-licensing, and general corporate development activities. The company currently markets Niaspan and Advicor for the treatment of cholesterol disorders, Azmacort for the treatment of asthma, Cardizem LA for the treatment of hypertension and angina, and Teveten and Teveten HCT for the treatment of hypertension. Kos has a strong and growing research and development pipeline, including proprietary drug delivery technologies in solid-dose, inhalation, and aerosol metered-dose device administration to help fuel sustained, organic sales growth into the future.

SkyePharma PLC develops pharmaceutical products benefiting from world-leading drug delivery technologies that provide easier-to-use and more effective drug formulations. There are now twelve approved products incorporating SkyePharma's technologies in the areas of oral, injectable, inhaled, and topical delivery, supported by advanced solubilization capabilities.

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MAP & Xemplar Sign Exclusive Manufacturing Deal for Innovative Tempo Inhaler Products

MAP Pharmaceuticals, Inc., a leading developer of novel inhaled drug therapies, and Xemplar Pharmaceuticals LLC, a contract services company developing inhalation products, recently announced the signing of an agreement under which Xemplar will serve as the exclusive manufacturer of MAP's proprietary Tempo Inhaler products. Under terms of the agreement, Xemplar will also be responsible for additional development activities, including process engineering for MAP's preclinical and clinical products.

"After examining a variety of commercial manufacturing options, MAP decided that expanding its current developmental relationship with Xemplar best serves the company strategically," said Timothy Nelson, CEO of MAP Pharmaceuticals. "Xemplar has proven to be a high-quality and reliable commercial supplier, and we are especially pleased by the company's willingness to provide MAP a priority manufacturing position within its operations."

As part of the agreement, MAP will provide an interim, interest-free loan, as well as funding for technical assistance to Xemplar to support the expansion of the company's existing production facility. Xemplar will add approximately 12,000 square feet of commercial space designed specifically for the production of pressurized metered dose inhaler products, nasal sprays, and dry powder inhalers.

Xemplar President Charles Eck and partners John and Richard Armstrong concur, "This agreement with MAP Pharmaceuticals is an exciting opportunity for both companies to make a significant step forward to reach their individual goals." Charles Eck addedd, "Xemplar will now be able to provide necessary services to the pharmaceutical aerosol industry and at the same time, MAP will secure their product development and commercial needs. We at Xemplar celebrate this union."

Xemplar's initial product manufacturing activities are focused on Tempo Migraine, MAP's proprietary therapy for the treatment of migraine. Presently in Phase I clinical development, MAP expects to advance the product into Phase II trials in the US later this year. Xemplar will also be responsible for manufacturing additional Tempo-based therapeutics presently under development at MAP. These include products featuring a respiratory drug for the treatment of asthma and chronic obstructive pulmonary disease (COPD), as well as a drug commonly delivered systemically to treat metabolic disease.

Genzyme & Brookwood Pharmaceuticals Enter Broad Collaboration in Drug Delivery With an Initial Focus on Peptides

Genzyme & Brookwood Pharmaceuticals Enter Broad Collaboration in Drug Delivery With an Initial Focus on Peptides

Genzyme Pharmaceuticals, a business unit of Genzyme Corporation, and Brookwood Pharmaceuticals, Inc., recently announced a broad collaboration to develop novel drug delivery solutions, with an initial focus on peptide delivery. The partnership offers customized solutions for parenteral formulations by combining expertise in design for peptide delivery, peptide synthesis, and drug delivery technologies.

The Design for Peptide Delivery approach optimizes peptide physical and chemical properties early on in drug development, so as to match a peptide with the properties of microparticles, implants, and other drug delivery formulations required for optimal drug delivery. Combining the capabilities and knowledge of Genzyme and Brookwood in parallel design of peptide and delivery systems will result in clients developing sophisticated pharmaceutical products that will benefit the patient.

"Brookwood Pharmaceuticals' scientific team has industry-leading experience in a wide range of drug delivery systems, with particular depth in long-acting parenterals, such as microparticles and solid implants," said Dan Hayden, Senior Vice President and General Manager of Genzyme Pharmaceuticals. "Combining Brookwood's strengths with Genzyme's expertise in custom GMP peptide development and manufacturing provides a powerful service to peptide drug delivery customers." In the longer term, many new and important drug delivery technologies can be developed from the portfolio of novel materials and technologies owned by Genzyme and Brookwood.

"By working with an industry leader like Genzyme, we envision this collaboration to generate plenty of energy, creativity, and new drug delivery solutions and products, from which our clients will greatly benefit," said Arthur Tipton, PhD, President and CEO of Brookwood Pharmaceuticals. "From our experience in peptide delivery, we have learned that focus on peptide modification and peptide properties can greatly aid in the stability and performance of a peptide drug delivery product."

Rather than promoting a specific technology, the Genzyme-Brookwood collaboration will offer customers a solution-oriented approach through synergistic capabilities and technologies, depending on the peptide and the customer's target drug profile. Customers will also benefit from enhanced capabilities and services, such as research-scale peptide synthesis for backbone and side chain modifications, evaluation of available drug delivery technologies, large-scale peptide drug substance production, formulation feasibility studies and development of micro-encapsulation processes, drug excipients manufacturing (phospholipids and polymers), drug product formulation, and manufacturing of clinical supplies, and final drug delivery product.

Market News and Trends

Acrux Announces Positive Phase III Results for Menopause Spray

Acrux recently announced positive results in a US Phase III clinical trial of Evamist, its daily skin spray for prevention of symptoms associated with menopause. The trial was conducted by its US commercial partner Vivus, Inc., which will now proceed to file a marketing application with the US FDA in the second half of 2006.

Evamist is the most advanced commercial application of Acrux's patented delivery technology. If the FDA approves Vivus' marketing application, Acrux's first product could be available to women in the US in the second half of 2007.

The Phase III trial assessed the safety and efficacy of Evamist for the treatment of hot flushes in menopausal women. The trial was a 12-week study of 457 menopausal women, conducted under a Special Protocol Assessment (SPA) from the FDA. Results showed that the most effective Evamist dose decreased the number of hot flushes by 78%. The reduction in frequency and severity of moderate-to-severe hot flushes was statistically significant compared with placebo for all three doses of Evamist evaluated. Importantly, application site irritation was less than 1% and was mild in nature.

"We believe these positive trial results along with this novel patient-preferred transdermal delivery system will establish Evamist as a superior estrogen therapy for the treatment of menopausal symptoms," stated Leland Wilson, President and Chief Executive Officer for VIVUS. "We have worked diligently toward the development of this unique and easy-to-use product, and we are thrilled with the efficacy and safety demonstrated in this trial. We now look forward to filing an NDA for Evamist in the second half of 2006."

Professor Alastair MacLennan, Joint Editor-in-Chief of Climacteric, the Journal of the International Menopause Society, and a member of Acrux's Scientific Advisory Board, commented, "Evamist could provide an attractive new option for millions of women: a low-dose estrogen delivered in a simpler and more convenient way. These Phase III trial results demonstrate its efficacy in treating the key symptoms that may be suffered by this significant patient group."

Approximately 2 million American women turn 50 each year. Women naturally enter into menopause usually between the ages of 45 and 55; however, surgical menopause may happen at any age. Menopausal symptoms occur when the ovaries stop producing estrogen. Symptoms include hot flushes, discomfort or pain during sexual intercourse due to vaginal atrophy (thinning of the vagina), and changes in skin and hair. Annual sales of estrogen-only replacement therapies in the US are estimated to be approximately $1.4 billion. Sales have now resumed growth after a period of decline, as new data from the Women's Health Initiative study showed that estrogen-alone therapy resulted in no increased risk of coronary heart disease or breast cancer. Transdermal estrogen patches and gels currently sell approximately $0.3 billion per annum. Primary market research studies suggest that many women would prefer to use Evamist over patches, gels and tablets.

Evamist, like Acrux's other women's health products addressing contraception and decreased libido, is a small, hand-held, easy-to-use spray that is designed to provide an easy and convenient means to deliver a preset dose of estradiol, a naturally occurring estrogen, via the skin. Evamist is placed gently against the skin, and an actuator button is pushed, which releases a light spray containing a proprietary formulation of estradiol. Estradiol is released into the blood stream on a sustained basis over 24 hours, providing a practical and convenient once-a-day dosing regimen. Evamist is fast drying, non-irritating, and invisible after application. Studies have shown that once administered, Evamist's formulation is not affected by washing and does not transfer to partners. Evamist is easily titratable between one, two, and three sprays.

Vivus licensed Evamist for the US market from Acrux in February 2004. Vivus paid Acrux a licence fee of $1 million and will make further payments to Acrux totalling $4 million on filing and approval by the FDA of the US marketing application. Vivus is responsible for manufacturing, sales, and marketing in the US and will pay Acrux royalties on sales. Acrux retains rights for the rest of the world and is seeking commercial partners for major markets, including Europe.

BDSI Announces Study Results for BEMA Fentanyl

BioDelivery Sciences International, Inc., (BDSI), recently announced the results of a multiple dose pharmacokinetic study regarding the company's flagship BEMA Fentanyl product. The study demonstrated that mean plasma fentanyl concentrations are highly reproducible and show a linear increase with multiple doses, reflecting a very predictable dosage form. The BEMA drug delivery disc is a small, dissolvable polymer disc applied to the buccal membranes of the mouth. In the study, an open-label, multiple dose, three-period study was performed in healthy volunteers who received a single 600-microgram dose of BEMA fentanyl buccal disc in period 1, followed by another 600-microgram dose in period 2, and three sequential 600-microgram doses separated by an hour in period 3. The study demonstrates that administration of a second and third dose (1800 micrograms over a 2-hour period) results in a linear increase in plasma concentrations over the initial dose. Further, each of the single 600-microgram doses yielded 1 ng/mL reproducibly in all subjects, meaning plasma concentrations were very similar from patient to patient. BEMA Fentanyl is being targeted for the indication of "breakthrough" cancer pain. Within the global market, pain medication generates estimated annual sales of more than $24 billion. An estimated $2 to $4 billion is targeted at breakthrough pain, with BEMA Fentanyl's indication of breakthrough cancer pain being a subset of this market. BDSI estimates that BEMA Fentanyl will generate minimum annual peak sales of $250 million. The BEMA Fentanyl Phase III program is expected to be completed by the end of 2006.

Market News and Trends

pSivida Limited Announces Rights Issue to Fund Late-Stage Macular Edema Trials & Commencement of Pancreatic Cancer Trials

Global bionanotech company pSivida Limited recently announced details of a Non-Renounceable Rights Issue offering one new ordinary share for every eight shares held at May 22 (the Record Date) at an issue price of AU$0.60 per share. The issue price represents an 18% discount to the 30 days volume weighted average closing price (VWAP) on the ASX up to May 1 being the last trading day, and a 7% discount to the 5-day VWAP. Excluding the effect of vested options, which may be exercised prior to the Record Date, the Rights offering could result in the issue of up to 48.25 million new ordinary shares, raising gross proceeds of approximately AU$29 million (US $22m).

The Rights Issue has an incorporated top-up facility whereby eligible shareholders may apply for additional new ordinary shares in excess of their entitlement at the same price. The Rights Issue is not being registered in the US under the US Securities Act of 1933, as amended (the "Act"), or any US state securities laws, and Rights and Shares will not and may not be issued, offered, sold, or transferred in the US or to any US persons unless (i) they are registered under the Act or an exemption from the registration requirements of the Act is available, or (ii) the offer, sale, or transfer is performed in accordance with regulations under the Act.

The Rights Issue is not underwritten, but pSivida will seek to place any shortfall with institutional and sophisticated investor clients of its US-based Lead Manager, Janney Montgomery Scott LLC, and certain co-managers appointed for this issue. Any ordinary shares issued in the US in connection with the Rights Issue as a result of any shortfall will be issued in an unregistered action. These shares will not be registered under the Act and may not be offered or sold in the US absent registration or an applicable exemption from registration requirements.

Capital raised from this Rights Issue will primarily fund the Phase III clinical trials of Medidur for the treatment of Diabetic Macular Edema (DME), and Phase IIa clinical trials of the company's lead BioSilicon product, BrachySil, which is being developed for the treatment of inoperable pancreatic cancer. pSivida expects to receive a significantly greater return by funding the Medidur trials under the Co-Development Agreement to receive a profit share with Alimera Sciences rather than a straight royalty, which would be payable if it did not co-fund the trials.

The Record Date for the Rights Issue is May 22. It is expected that New Shares issued under the Entitlement Offer to eligible shareholders will be quoted on a deferred settlement basis on June 8 with normal trading for all New Shares issued under the Offer expected to commence as soon as practicable after that date. Further details on the proposed timetable for the Rights Issue will be set out in the prospectus. Any ordinary shares issued in the US in connection with the Rights Issue will be issued in an unregistered transaction. Applications are expected to close on June 7 (at press time).

A prospectus for the Rights Issue will be made available when the New Shares are offered, and applicants under the Rights Issue wishing to apply for New Shares will need to complete the application form that will be in or will accompany the prospectus.

Sirna Therapeutics Announces Programs in Strategic Research Alliance With GlaxoSmithKline

Sirna Therapeutics, Inc., a leading RNAi therapeutics company, recently announced that as part of its exclusive, multiyear collaboration with GlaxoSmithKline (GSK) in respiratory diseases, the companies have initiated programs in asthma and respiratory syncytial virus (RSV). As part of the respiratory collaboration, the companies also plan to pursue RNAi-based therapeutics against chronic obstructive pulmonary disease (COPD) and allergic rhinitis. Sirna will provide GSK with optimized and formulated siRNAs against targets for these diseases, and GSK will assume all responsibility for the further preclinical and clinical development of compounds that emerge from these programs.

RNA interference (RNAi) is a natural, selective process for turning off genes. Sirna designs and develops short interfering RNA (siRNA) compounds, which down regulate the expression of critical proteins responsible for viral replication and pathogenesis. GSK is a world leader in the discovery and development of treatments for respiratory diseases and has a wealth of expertise in inhaled and intranasal drug delivery technologies. Local delivery of siRNA to the respiratory tract will substantially enhance the feasibility of developing successful treatments with this exciting new platform technology.

"Sirna has demonstrated the ability to develop chemically modified and optimized siRNA compounds and then deliver those compounds effectively into the lung with our nanoparticle formulations," stated Barry Polisky, PhD, Chief Scientific Officer at Sirna. "Further, we have demonstrated that our proprietary approach to targeting the conserved region of a viral genome has resulted in significant viral knockdown in a non-human primate model. With these encouraging results and together with the combined efforts of Sirna and GSK scientific teams, we expect to expedite the development of novel RNAi-based therapies: those efforts initially focused on asthma and RSV."

Sirna is the first company to file enabling patents for over 250 important mammalian disease targets, including respiratory targets such as MMP-13, IL-4, IL-13, VCAM, and ICAM as well as antiviral targets, such as RSV. In addition, Sirna has been granted patent claims in the UK and has pending claims in the US that broadly cover any siRNA molecule that targets conserved sequences within a virus or a gene.

The World Health Organization (WHO) estimates the prevalence of COPD to be 600 million worldwide. By the year 2020, COPD is expected to be the third leading cause of death and the fifth leading cause of disability. Asthma currently affects 15 million people in the US, causes approximately 5,000 deaths per year, and accounts for an estimated $13 billion in annual healthcare costs. Allergic rhinitis (AR) affects approximately 20% of the US population. Over-the-counter treatments are estimated to be approximately $55 billion dollars per year and prescription medications exceed $6 billion per year worldwide. The financial impact of lost productivity is estimated to be $1.5 billion dollars per year. Respiratory syncytial virus (RSV) is a highly infectious agent affecting children under the age of 2. RSV can lead to serious lower respiratory infections, such as pneumonia, and can be fatal to infants born with lung or heart problems.

Market News and Trends

Transpharma Medical Receives First Milestone Payment From TEVA Pharmaceuticals

TransPharma-Medical Ltd., the Israeli-based biopharmaceutical company that develops pharmaceutical products utilizing its unique transdermal RF-MicroChannels transdermal drug delivery technology, recently announced it has received its first milestone payment from Teva Pharmaceuticals for successfully completing the first clinical trials, based on a joint development agreement originally signed between the two companies in 2004.

The milestone achieved is in line with the product development plan of the drug molecule, which is the first of up to five molecules designated for development by TransPharma and Teva in the 2004 agreement.

Under the agreement, Teva will exclusively market each of the drug-products and will pay TransPharma milestone payments, royalties, and development costs. The development process will continue to be carried out in close cooperation between the two companies.

"This first milestone achieved is proof of the great strides TransPharma has taken on the way to full development of its unique drug-products," said Daphna Heffetz, CEO of TransPharma. "It is a vote of confidence by a world leader in pharmaceutical development, manufacturing, and marketing, and it is evidence of the great potential inherent in our unique transdermal technology."

In the coming years, TransPharma will continue working closely with Teva on the development of the specified molecules, as well as planning to ally with other companies for developing additional drug-products. In parallel to its allied products, TransPharma is developing its own proprietary product pipeline.

Established in 2000, TransPharma Medical Ltd. is a biopharmaceutical company focusing on transdermal delivery, bringing to market technologies that increase the portfolio of drugs delivered via a patch. TransPharma has developed a unique and clinically proven transdermal drug delivery system, ViaDerm. The system is based on TransPharma's RF-MicroChannels technology that creates microscopic passageways through the outer layer of the skin, allowing for therapeutic administration of a wide variety of drugs from a patch. Currently available systems are limited to delivery of small-size drug molecules. ViaDerm overcomes these limits, enabling delivery of a large variety of drugs, including proteins in a pain-free, low-cost, user friendly manner.

FDA Grants Fast-Track Designation to Nektar's Amphotericin B Inhalation Powder

Nektar Therapeutics recently announced the US FDA has granted Fast-Track designation to Amphotericin B Inhalation Powder (ABIP) for prevention of pulmonary fungal infections in patients at risk for aspergillosis due to immunosuppressive therapy, including those receiving organ or stem cell transplants, or treated with chemotherapy or radiation for hematologic malignancies (leukemias). The FDA granted Fast-Track designation for significant reasons.

Invasive aspergillosis is a serious infection that usually affects immunosuppressed patients receiving organ or stem cell transplants, or treated with chemotherapy or radiation for hematologic malignancies. The infection is often lethal in medically immunosuppressed patients. There is no approved agent for prevention of pulmonary fungal infections in patients at risk for aspergillosis due to immunosuppressive therapy, including those receiving organ or stem cell transplants, or treated with chemotherapy or radiation for hematologic malignancies. Therefore, there is an unmet medical need for a new treatment. Fast-Track designation allows the FDA to expedite the review of new drugs that are intended for serious or life-threatening conditions and that demonstrate the potential to address unmet medical needs. An important feature of Fast-Track designation is that it emphasizes the critical nature of close, early
communication between the FDA and the sponsor company to improve the efficiency of product development. Under Fast-Track, Nektar is now eligible to submit portions of the marketing application for review on a rolling basis prior to completion of the final registration package for the product.

"We are pleased the FDA recognizes that Nektar's product for this indication meets the criteria for Fast-Track designation, and this is an important step toward providing a much-needed medical solution to protect against life-threatening pulmonary infections," said Dr. David Johnston, Nektar Senior Vice President of Research and Development. "Our product could represent a major paradigm shift in antifungal therapies as we aim to prevent infections by targeting the lungs directly and therefore avoid the serious systemic and dose-limiting side effects of intravenous and oral therapies. We look forward to working closely with the FDA through the development process."

Nektar announced in February 2006 that the FDA had granted US orphan drug designation to ABIP for the prevention of pulmonary fungal infections in patients at risk for aspergillosis due to immunosuppressive therapy. The Orphan Drug Act provides a 7-year period of exclusive marketing to the first sponsor who obtains marketing approval for a designated product for the designated indication.

Market News and Trends

Cardinal Health, Inc. (CAH) Receives Frost & Sullivan Best Bang For The Buck Award For Its Cost Efficient Manufacturing

Frost & Sullivan selected Cardinal Health, Inc., as the recipient of its 2006 Best Bang for the Buck Award in the global pharmaceutical contract manufacturing markets.

Each year, this Award is presented to a company that has provided customers with the solution and/or service that provides the highest ratio of value to cost. The recipient has provided customers with a product that provides quality, while staying extremely competitively priced. Cardinal Health is the largest global contract manufacturer serving the pharmaceutical and biotechnology industries. It also offers the broadest range of manufacturing options, including oral dosage forms, and sterile and topical products.

"What differentiates Cardinal Health from numerous other contract manufacturing organizations is its ability to move beyond typical manufacturing services and offering unique solutions to its clients, thereby leveraging its value proposition," says Frost & Sullivan Research Analyst Barath Shankar S. "Cardinal Health holds more than a thousand patents and applications in drug delivery technologies that enable pharmaceutical and biopharmaceutical companies to relaunch their existing products using these novel delivery technologies, helping revive late life-cycle products."

In the oral dosage form segment, Cardinal Health offers novel proprietary drug delivery techniques through their softgel capsules, Zydis (a fast-dissolving dosage form); EnCirc, EnVel, and EnSolv (oral modified-release formulations); and controlled-release formulations.

In the sterile products segment, Cardinal Health offers sterile fill/finish, blow/fill/seal and lyophilization services, catering to clients from preclinical to commercial stages. In the topical products segment, Cardinal Health provides novel technologies, such as the Microsponge timed-release and DelPouch unit-dose delivery systems to clients who wish to manufacture and market their own compounds as innovative products.

Apart from manufacturing, Cardinal Health also offers packaging services that enable pharmaceutical and biopharmaceutical companies to increase their brand awareness by improving their presence and patient compliance. Cardinal Health, which offers a one-stop-shop solution service, has been able to gain visibility and reputation as a solution provider among companies.

Similarly, mid-size and specialty companies that need multiple sources in their supply chain consider Cardinal Health an ideal replacement for multiple supplier chain. Cardinal Health is expected to function as a single supplier catering to almost the entire supply chain. The post-launch support by Cardinal Health includes life-cycle management, which ensures increased product profitability from its services.

"One of the key competitive advantages that Cardinal Health has acquired is the continuous interaction and the communication path it has established with pharmacists and physicians," notes Mr. Shankar. "As a result, Cardinal Health has been able to stay up-to-date with trends in the industry and offer solutions to its clients to stay competitive and grow their businesses successfully."

Eurand Initiates Second of Two Phase III Studies for EUR-1008 in Patients With Pancreatic Insufficiency

Eurand recently announced the initiation of the second of two Phase III clinical trials required for registration of its pancreatic enzyme product (PEP), EUR-1008, in patients with exocrine pancreatic insufficiency (EPI). EPI is a deficiency of digestive enzymes normally produced by the pancreas that leads to malnutrition, impaired growth, and shortened life expectancy. EPI can result from a number of diseases and conditions, including cystic fibrosis (CF), chronic pancreatitis, and pancreatic cancer.

The trial is designed to determine the safety and tolerability of EUR-1008 in children under the age of 7. The trial will involve approximately 10 clinical study sites in the US. Patient enrollment has commenced and is expected to be complete by end of the third quarter 2006. Results of the study are expected in the fourth quarter of 2006. The protocol for the trial has been prepared in collaboration with the Cystic Fibrosis Foundation Therapeutic Development Network.

EUR-1008 is a new and proprietary PEP developed by Eurand. It has been developed as a delayed-release capsule intended to provide consistent product dosing over time, and EUR-1008 will be available in multiple dosage strengths to provide flexibility and convenience in dosing. A low dose, microtablet formulation has been specifically developed for young children.

Dr. Jamie Wooldridge MD, Assistant Professor of Pulmonary Medicine at Children's Hospital Medical Center, Cincinnati, Ohio, and Lead Investigator for the trial commented, "The correct treatment of pancreatic insufficiency is fundamental to the management of cystic fibrosis in young children, this pediatric trial will further evolve our understanding of the disease and how best to treat our patients."

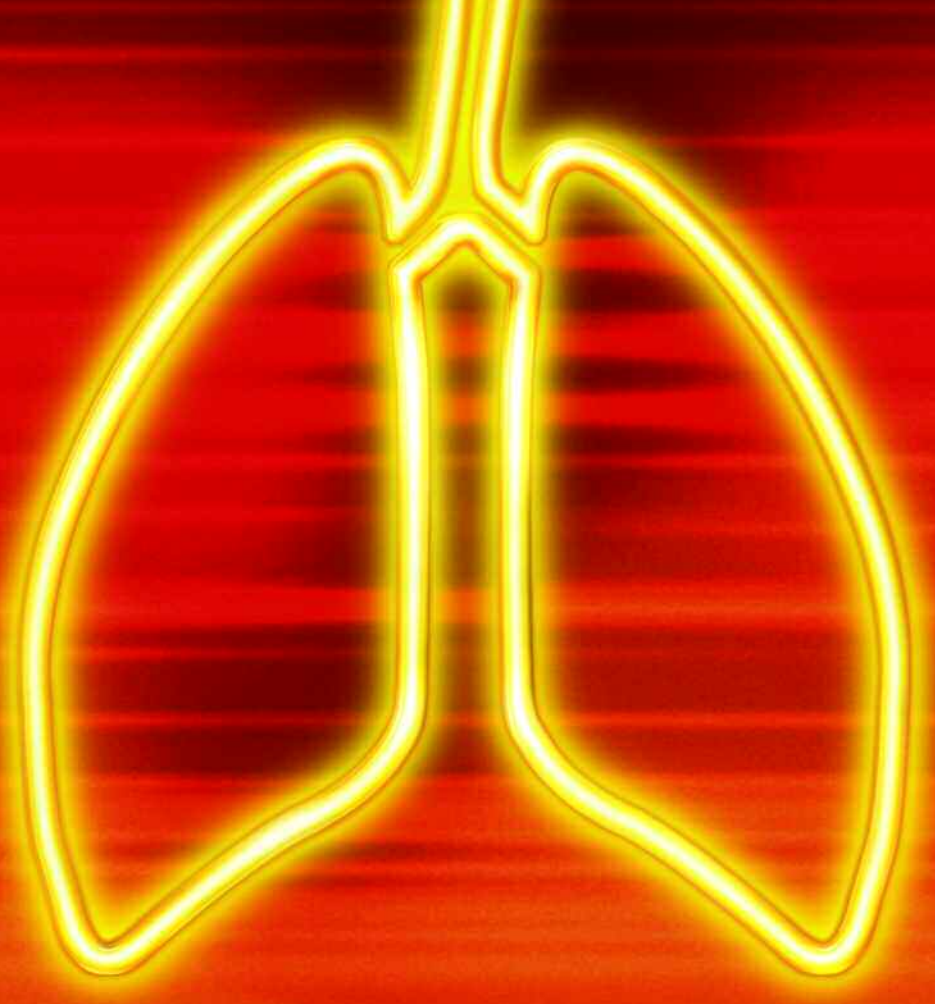
The Phase III trial will be conducted in CF care centers in the US. The study will be a multicenter, open label trial in patients under 7 years of age with pancreatic insufficiency and cystic fibrosis. The study will evaluate the safety and efficacy of EUR-1008 in improving fat absorption, while assessing among other endpoints, improvements in protein and other nutrient absorption.

EUR-1008 is a new orally delivered pancreatic enzyme product consisting of approximately 14 enzymes, coenzymes, and cofactors. It is biologically similar to endogenous human pancreatic secretions and is intended to treat malabsorption of fats, proteins, carbohydrates, and other essential nutrients in patients with pancreatic insufficiency. EUR-1008 is a highly stable formulation that has been developed to meet US FDA) guidelines for pancreatic enzyme products. EUR-1008 is being developed in a number of dosage forms and strengths that Eurand believes will provide consistent product dosing, stability, long-term shelf-life, and convenient dosing.

Current treatment of pancreatic insufficiency requires the use of pancreatic enzyme products. None of the currently marketed products in the US have been approved by the US FDA. The FDA has issued regulations requiring all PEPs marketed after April 2008 to have an FDA-approved registration. Eurand is conducting two Phase III trials in support of registering EUR-1008 for the treatment of exocrine pancreatic insufficiency.

"With our first EPI trial up and running, we are delighted to announce the commencement of patient recruitment for this our second trial," commented Gearoid Faherty, CEO of Eurand. "We believe that this trial, in which all of the patients will be less than 7 years old, will be the first such trial of this design to be conducted in the US in over 15 years. As children represent a significant part of the EPI patient population, it is vital that we understand how these drugs perform in this patient group."

EPI is a deficiency of digestive enzymes normally produced by the pancreas that leads to malabsorption of fats, proteins, carbohydrates, and other essential nutrients. Impaired absorption can result in malnutrition and a host of secondary complications, including retarded growth and development, impaired immune response, infections, and shortened life expectancy among others. EPI can result from a number of diseases and conditions, including cystic fibrosis, chronic pancreatitis, and pancreatic cancer.



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Parameters of Value - Drug Delivery Companies

By: Josef Bossart, PhD

If you haven't yet, set aside some time to read the 2005 best-seller Freakonomics by Steven Levitt and Stephen Dubner. It's a book that takes you on an interesting trip through urban legend and common sense beliefs to reveal some not so obvious relationships. Two concepts from this book, correlation and causality, are the stimuli for this article. Correlation and causality refer to the relationship between any series of events or actions and the impact any one of these events or actions has on another. Let's see if we can find any correlation or causality between corporate development activities undertaken by drug delivery companies and the valuation given to these companies by the market.

By looking at some of the common sense parameters that one usually associates with enhanced corporate value, partnerships, pipeline, revenue, and profitability, perhaps we can discover which have the greatest impact on company value. Are you running ahead of me and thinking that there isn't any relationship to be found because the market really can't fairly value a company if it doesn't understand the business and the "true" value points? Well, we had better hope we can find some correlation or causality. If we can't, it will mean that any and all corporate actions undertaken by a drug delivery company are equally valid and no better than regular 3-hour lunches.

Let's start with a couple of qualifiers. This article is not meant to provide a comprehensive review of all drug delivery companies using rigorous statistical analysis. Nor is it meant to provide a definitive diagnosis or prescription for drug delivery company corporate development activities. Rather, the article hopes to provide a starting point for your own investigation of high-value strategies for the drug delivery industry. At best, you may find threads that lead you to a winning strategy; at worst, I hope it will make you evaluate your current corporate activities and see if they are anything more than applied common wisdom.

The second qualifier is that the companies discussed in this article were chosen for no particular reason. The six companies cover a broad range of drug delivery technology platforms, market capitalizations, and strategic directions. The only conscious decision in selecting these companies was to focus on public drug delivery companies for which reasonably full disclosure is available.

All of the data presented in this article were sourced from non-confidential sources that include SEC filings, press releases, company presentations, published interviews, and financial analyst reports.

CAST OF CHARACTERS

The companies selected for this article are listed in Table 1 along with their key platform technologies, founding date, and current corporate strategy. These companies will be familiar to the reader. The founding date listed refers to the founding of the first iteration of the company. The most unusual example will be the 1983 date for SkyePharma. This dates back to the formation of Jago by Jacques Gonella and commercialization of the Geomatrix oral drug delivery technology. This Jago asset was the foundation of SkyePhama, which as a corporation prior to the acquisition of Jago in 1996, supplied structures for outdoor events (think tents for weddings and receptions). SkyePharma thereafter grew by further acquisitions to encompass a wide variety of drug delivery technology platforms.

Not included are the drug delivery giants Alza and Elan. Both of these companies are now relics of the great drug delivery decades of the 80s and 90s. Elan wandered far from its drug delivery roots in the late 90s and Alza, after its remarkable success with oral and transdermal drug delivery, evolved into a specialty pharmaceutical company that was acquired in 2001 by J&J.

All of the companies included in this review continue to practice, at least in part, the traditional model of drug delivery by providing drug delivery technology to third parties for the development of biopharmaceutical products. In many cases, these companies also label

Would you like to convert your drugs from IV to subcutaneous (SC) delivery or enhance the dispersion of your existing SC compounds? With Enhanze™ Technology, microgram quantities of a fully human recombinant enzyme act as a "molecular machete" to clear the subcutaneous "jungle." Based upon this mechanism of action, co-delivery with Enhanze is anticipated to permit the SC administration of large volumes of antibody drugs, speed onset of action relative to SC delivery without Enhanze, and improve patient comfort. Backed by a robust IP portfolio, Enhanze may extend a compound's patent life and potentially reduce COGS for products that are expensive to manufacture.

Enhanze Technology employs the first and only human recombinant enzyme for injectable drug dispersion. The enzyme in Enhanze has been used in two FDA-approved formulations. Enhanze is being developed to deliver an optimized pharmacokinetic profile and thus offers a potential competitive advantage for partners' products. Potential benefits of this technology include:

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- Dispersing drugs away from injection site, potentially reducing concentration-dependent injection site reactions
- Compared to SC administration without Enhanze, reducing Tmax and increasing bioavailability for large molecule compounds
- Enabling conversion of certain IV drugs to SC self-delivery

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themselves as specialty pharmaceutical companies, with the implication that they intend to develop and market their own products. The hybrid strategy for these drug delivery/specialty pharma companies seems to involve picking up traditional drug delivery partnering deals that help cover operating expenses while they develop products for their own commercialization. This is a strategy popularized by Alza, Elan, and Biovail as they pushed beyond being technology and product providers.

THE PARAMETERS

There are dozens of parameters we might consider as points of analysis for these companies, as well as any number of time intervals. To make the analysis more relevant, we will look at the time period of 2001 to 2005. This 5-year window should provide sufficient time to let a company's market performance respond to its corporate development actions. The 2001 and 2005 markets are also similar enough, at least in terms of the market index prices, to rule out any major market swing effect.

So, with a defined period, we need to consider the parameters of performance that might impact market capitalization. Market capitalization as used in this article refers to average capitalization for any year as determined by averaging the yearly high and low, and multiplying by the shares outstanding at year's end. This figure may not be the closing value for the year, but reasonably captures the ups and downs of the company in a single figure. It's interesting to note that most of the companies were on a roller coaster in terms of stock prices and market cap. While inter-year market capitalization variation might be less than 100%, the intra-year swings for these companies could exceed 500%. While this provides an interesting opportunity for day traders, it only causes anxiety for longer term investors.

The performance parameters included in Table 2 include the number of marketed products in 2001 and 2005, the clinical stage partnered and unpartnered products, as well as revenue and profit (actually losses except for one company). These seem the most common sense parameters to consider as surrogates for corporate performance (there it is again, common sense). Approved products provide insight into the real-world performance of the technologies, clinical stage products provide a promise of future licensing and royalty income, and partnered products indicate third-party validation of the technology and company. Revenue similarly provides a measure of the real-world interest and acceptance of a company's technology platforms. Profit should be the best measure of performance, but as we'll see, only one of the companies was able to provide consistent profitability in the period 2001 to 2005.

A couple of liberties have been taken with the information included in Table 2. The list of approved products includes me-too type products, even if they formally are not generics. These include knock-offs of extended-release nifedipine (SkyePharma and Penwest) and transdermal estradiol (Noven). And the 2005 financial information for Alkermes, the only non-calendar year company, is a hybrid of two financial accounting periods, the first through third quarters of their 2006 fiscal year (April to

TABLE 1 - PLATFORMS & STRATEGIES

COMPANY	DATE FOUNDED (PREDECESSOR)	PLATFORM TECHNOLOGIES	STATED STRATEGY
Alkermes	1987	Oral Inhalation	Drug Delivery Drug Delivery Plus Specialty Pharma
Durect	1998	Injectable, Oral, Transdermal	Specialty Pharma Drug Delivery
Nektar	1990	Inhalation, Injectable	Drug Delivery Drug Delivery Plus
Noven	1987	Transdermal	Drug Delivery Specialty Pharma
Penwest	1991 (Edward Mendell Co.)	Oral	Drug Delivery Drug Delivery Plus Specialty Pharma
SkyePharma	1983 (Jago)	Oral, Inhalation, Injectable	Drug Delivery Drug Delivery Plus Specialty Pharma

Drug Delivery: Licensing of technology and development of partnered products. **Drug Delivery Plus:** Development of products using company technology for later-stage partnering. **Specialty Pharma:** Sales and marketing of biopharmaceuticals by company.

TABLE 2 - KEY COMPANY INFORMATION

	YEAR	NEKTAR	DURECT	ALKERMES	SKYEPHARMA	PENWEST	NOVEN
Averaged Market Cap	2001	$1,607 MM	$426 MM	$1,755 MM	$595 MM	$213 MM	$642 MM
	2005	$1,456 MM	$269 MM	$1,429 MM	$599 MM	$323 MM	$355 MM
Approved Products (Knock-Off)*	2001	3	0	1	9 (4)	2 (1)	4 (2)
	2005	7	0	2	14 (4)	2 (1)	4 (2)
Clinical Stage Pipeline	2001	17	1	9	12	2	4
Partnered Products	2001	15	0	6	9	2	1
Internal Products	2001	2	1	3	3	0	3
Clinical Stage Pipeline	2005	11	4	5	12	10	3
Partnered Products	2005	9	3	4	9	1	3
Internal Products	2005	2	1	1	3	9	0
Late Stage Set-Back*		-	Yes	-	-	-	Yes
Annual Profit (Loss)	2001	($250 MM)	($18 MM)	($61 MM)	(£9 MM)	($23 MM)	$10 MM
	2005	($185 MM)	($45 MM)	($15 MM)	(£51 MM)	($16 MM)	$12 MM
Revenue	2001	$77 MM	$7 MM	$54 MM	£46 MM	$40 MM	$46 MM
	2005	$126 MM	$29 MM	$136 MM	£61 MM	$6 MM	$53 MM

*See text for explanation

December 2005) and the fourth quarter of their year 2005 (January to March 2005). The other years' figures for Alkermes correspond to their annual year (April to March).

ANALYSIS

It's not obvious where to start in looking for potential correlations and causality. A simple analysis of the key performance parameters of Table 2 is provided in Table 3. These figures include compiled profit and revenue growth over the 5-year period, a rough analysis of changes in pipeline products and partnerships, and of course the change in market capitalization.

Beyond this, any analysis seems to require equal attention to the qualitative aspects of each company's performance over the 2001 to 2005 period. But these can become issues of subjectivity and open to disagreement and challenge. Is one pipeline really that much better than another? Is it better to have two potential $500-million products at Phase I than one $100-million product at Phase III? It's a tough call, and one that's worth looking at if the hard numbers don't reveal anything.

OBSERVATIONS

Well, I'm having a hard time finding any correlation much less causality between the relative performance of these six drug delivery companies, and their activities over the past 5 years. The one company that has shown profitability for each of the 5 years sports the largest market capitalization drop (Noven, -45%), and the company with the biggest revenue drop (subsidiary sale) shows the largest market capitalization gain (Penwest, +43%). The two giants of the group, Alkermes and Nektar, moved sideways in terms of market capitalization but not in losses. Nektar leads the charge with a cumulative loss of $710 million. Alkermes is a distant, but still significant second, with losses of $360 million. On a percentage basis, Nektar and Durect lead the group in terms of cumulative losses relative to their 2005 market capitalization, at about 50%, although only Durect has suffered a significant market cap drop.

The pipeline trends don't seem to tell us much more than the financial figures. Penwest and Durect were the only companies to expand their pipelines, yet their market caps went in different directions with Penwest showing the highest increase and Durect the largest drop. This is despite the qualitative observation that Durect added external, presumably validating, partnerships while Penwest's pipeline increase came from multiple early clinical stage internal projects.

Is there some relation between market capitalization and company validation as provided by approved products? The only company without an approved product using their technology, Durect, also sports the lowest market capitalization. But Nektar, with seven approved products (perhaps more realistically five if you eliminate two for which

they are primarily a raw material supplier), has a market capitalization twice that of SkyePharma, which has 14 approved products, 10 if you disregard their me-too products.

Perhaps any sense of a correlation is skewed by the later-stage product failures reported by Noven and Durect in the past 24 months. These are the two companies with the largest capitalization drop of the group. In the case of Noven, their ANDA version of Duragesic was rejected by the FDA, with the understanding that a new formulation would be required to secure ANDA approval. Durect's challenge related to a failure of their Chronogesic implant to perform as expected in late-stage clinical trials necessitating a system redesign. The relationship of Durect's Chronogesic set back to its market cap drop is not obvious as the suspension of Phase III trials was announced in mid-2002, while their market cap only bottomed out in the first quarter of 2003. Noven in contrast seemed to be hurt more by the Women's Health Initiative Study results that questioned the benefits of hormone replacement therapy than any loss of a pipeline product. The remaining companies, while not suffering anything of this magnitude, did have their challenges.

Nektar's Exubera underwent a high level of investor and regulatory authority scrutiny before receiving tentative regulatory approval in the second half of 2005. Alkermes had generally positive product outcomes over the 5-year period with Risperdal Consta approved worldwide and Vivitrol receiving an approvable letter from the FDA. This was tempered by the withdrawal of their first approved product, Nutropin Depot, from the market in 2004. There was also the ill-fated Reliant pharmaceuticals acquisition attempt that could not have helped corporate valuation.

Penwest, while not having a definitive regulatory failure decided to terminate activities related to FDA approval of its late-stage sustained-release formulation of metoprolol following a non-approval letter. SkyePharma reported no significant pipeline failures in the 5-year period, although its product approvals were limited to highly specialized market indications.

REFLECTIONS

No hits, no runs, no one left on base. Nothing in this little exercise has provided me with any insight into a performance parameter, or parameters, that correlate with market capitalization. It's pretty obvious that the larger companies in terms of pipelines, partnerships, revenue, and losses have a larger market capitalization than the smaller firms. But it's not really apparent whether these companies have a larger market capitalization because they have bigger operations, or whether they have bigger operations because they have a higher market cap and receive more funding to support them.

So, as the head of business and/or corporate development, what would you suggest to your CEO and Board as the best strategy to increase company value? Don't try and wriggle out of the question by suggesting that there is a disconnect between real corporate value and how the market recognizes it. The market can be wrong from time-to-time, but over a 5-year period, they generally get it right. Would you propose increasing the burn to build a larger pipeline that can be translated into a

TABLE 3 - KEY PARAMETER CHANGES 2001-2005

	NEKTAR	DURECT	ALKERMES	SKYEPHARMA	PENWEST	NOVEN
Cumulative Profit Gain (Loss)	($710 MM)	($150 MM)	($360 MM)	(£127 MM)	($96 MM)	$58 MM
Market Cap. Change	-9%	-37%	-19%	+1%	+43%	-45%
Cumulative Profit/2005 Market Cap	-0.49	-0.56	-0.25	-0.21	-0.30	+0.16
Revenue Change % **Revenue Change $**	+64% +$49 MM	+300% +$22 MM	+152% $82 MM	+33% £15 MM	-85%* -$34 MM	+15% +$7 MM
Profit Change (2005/2001)	+26%	-60%	+75%	-467%	+30%	+20%
Pipeline Change **- Partnered** **- Internal**	-35% -40% 0%	300% 1000% 0%	-44% -33% -67%	0% 0% 0%	400% -50% 1000%	-25% 200% -100%
Market Cap 2005	$1,456 MM	$269 MM	$1429 M	$599 M	$323 M	$355 MM

*See text for explanation

greater market value? Durect increased their burn and lost value while Penwest decreased their burn and raised value; and both companies increased their pipelines. What about suggesting an investment in building a pipeline of products for your company's own account for later-stage partnering and greater rewards? Well, you could be on the right track, but you would be heading in a different direction than the majority of these companies that have trimmed down their pipeline of clinical products.

Adopting actions to achieve and maintain profitability would seem to be an obvious strategy; although how to make the leap from losses to profits seems to be a huge challenge. But even this appears to be at odds with what we see with our six-company sample. The only consistently profitable company, Noven, has the third lowest market capitalization and has suffered the largest drop in value over the 5-year period.

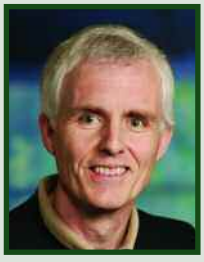
Wait, maybe the answer is too obvious; transform into a specialty pharmaceutical company. Specialty pharma companies get more respect and higher valuations than drug delivery companies, don't they? Assuming this is correct, most of the companies in our sample seem to think so, we are faced with the challenge of jumping from drug delivery to specialty pharma. Do we focus on enhancing the internal pipeline, while incurring the much greater losses that come with holding on to products longer? Or do we graft on a sales and marketing function to sell the products we intend to in-license as a jump start to the business? Exactly how does a drug delivery company become a successful specialty pharmaceutical company?

Damned if you do, and damned if you don't. Both Alkermes and Nektar seem to be intent on transforming their business model. Alkermes refers to itself as a pharmaceutical company with proven proprietary drug delivery systems. Holding an FDA approval for its first pipeline product, Vivitrol, and retained promotion rights in the US, Alkermes seems to be on the way to reaching its goal. With a market cap that has been hovering around the $2.2-billion mark for the past few months, it seems they are ready to stay above the unofficial $2-billion ceiling for drug delivery companies. Let's see how the market responds when Alkermes achieves sustained profitability and it is valued on the basis on earnings and earnings growth. Hopefully they can mimic the success of Celgene, a specialty pharmaceutical company that has grown from a market cap of $2 billion to $13 billion with a modest pipeline, current annual sales of about $500 million, and a P/E of more than 200.

Nektar seems to be a few steps behind Alkermes in capturing greater market value from their more traditional drug delivery base. Recent press releases hint at Nektar's interest in a proprietary pipeline but don't clarify exactly what they intend to do with it. With their lead proprietary product in Phase II testing, it will be some time until they need to make a declaration on their commercialization intent. In the meantime, Nektar will need to look to Exubera becoming a huge success if they hope to take on internal pipeline development expenses while reducing their annual losses.

Wow, it seemed so easy when reading *Freakonomics* to "see" the web of correlations and causality in areas of our everyday life. But when we look at something we should already understand, we find the correlations and causality can't be found. Does that mean they don't exist, or does it mean we aren't looking in the right places? I prefer to believe in the latter, and I'm going to keep on searching. But because I haven't found any better strategy that correlates with market success, perhaps I'll try that 3-hour lunch suggestion. ◆

BIOGRAPHY



Dr. Josef Bossart is Founder and Principal at Bossart4 Bioconsult (www.b4bio.com), a business development services company that provides strategic and transactional advice to biopharmaceutical companies. Dr. Bossart has more than 25 years of global biopharmaceutical experience in the areas of business development, strategy, operations, as well as sales and marketing. His biopharmaceutical company experience includes, most recently, executive positions at Enzon Pharmaceuticals and GeneMedicine, Inc. Prior to that, he spent 15 years within the Rhône-Poulenc Rorer group, lastly as 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, and his BSc (Hon.) in Chemistry from Carleton University.

ATTORNEY REVIEW

Compliance Failures – The Government Comes Out Swinging

By: Mr. Sanjay ("Jay") Sitlani

If recent enforcement actions by the federal government against pharmaceutical firms for regulatory compliance failures are any indication, federal scrutiny of such failures may result in stricter penalties. While strict federal enforcement actions are expected against those pharmaceutical manufacturers who fail to comply with the law, many industry analysts are nonetheless surprised at the change in enforcement and compliance strategies employed by the federal government, as well as the heightened scrutiny by the FDA. In particular, two recent and well publicized enforcement actions by both the United States Department of Justice (DOJ) and FDA are testament to this observation. As these enforcement actions cover the entire spectrum of the process of bringing a pharmaceutical to market, namely manufacturing and marketing, pharmaceutical manufacturers are forewarned that government oversight and review of the pharmaceutical industry remains a force to be reckoned with.

The first case involves not only the largest single settlement to date involving off-label drug promotion ($704 million to be exact), but also indicates that the DOJ is firmly in control of enforcement against those pharmaceutical firms that engage in statutorily prohibited off-label promotion of their drugs. Coming on the heels of a $430-million settlement in 2004 between the federal government and Pfizer, Inc. (Pfizer) involving off-label promotion of the drug Neurontin®, the DOJ announced on October 17, 2005, that Serono S.A. (Serono) would pay $704 million to settle civil allegations and criminal charges related to the marketing of its anti-AIDs wasting drug, Serostim®. Much like the earlier Pfizer settlement, the Serono settlement also includes a corporate integrity agreement (CIA) with the Department of Health and Human Services' Office of the Inspector General (OIG). However, the Serono settlement differs significantly from the Pfizer settlement in that unlike the Pfizer settlement, it relies more on heavy civil penalties and a CIA than criminal pleas.

The Serono matter first appeared on the DOJ's radar in 2004 after former sales representatives filed three *qui tam* complaints against Serono and its various subsidiaries, alleging violations of the False Claims Act (FCA) resulting from Serono's unlawful marketing practices of Serostim, a drug approved for the treatment of AIDs wasting. *Qui tam* or whistleblower provisions authorize a private citizen to bring an action on behalf of the government for violations of specific statutes. The Serono whistleblowers alleged that Serono knowingly caused false or fraudulent claims to be submitted for reimbursement by Medicaid, by expanding the indication for which Serostim was approved, thus engaging in unlawful off-label promotion of the drug. Specifically, the complaints alleged that Serono sales representatives attempted to promote Serostim for lipodystrophy, an unapproved use distinctly different from AIDs wasting syndrome, and that they had attempted to expand the definition of AIDs wasting to include a loss of body cell mass (BCM) by the use of a bioelectrical impedance analysis (BIA) device. Changes in weight and lean body mass, and not BCM, were the criteria for AIDs wasting syndrome used in the clinical trials to support the FDA approval of Serostim, and the BCM software used in the BIA device had never been submitted to FDA for approval or premarket clearance. In spite of this, the complaints alleged, Serono sales representatives used the devices to perform BIA tests on patients, often interpreting test results for the purpose of diagnosing AIDs wasting and the subsequent use of Serostim. Moreover, the complaints also alleged that Serono engaged in garden-variety kickbacks through its "6m-6 Day Plan" in which sales representatives were offered financial incentives for meeting sales of $6 million in 6 days, who in turn offered physicians an all-expenses paid trip to a conference in France for prescribing Serostim.

Even prior to the DOJ's foray into the Serono matter, federal scrutiny of off-label drug promotion had been on the rise since 2003 when the OIG first began to include investigations of pharmaceutical fraud as its annual objectives, with an intent to more closely assess the FDA's oversight and review of off-label drug promotional practices. Thus, unsurprisingly, the Serono whistleblower complaints piqued the interest of the federal government already involved in investigating Pfizer's off-label promotion of Neurontin and the illegal kick-backs provided to physicians as part of these promotional activities. Moreover, the use of an unapproved diagnostic device to increase prescriptions and the concomitant kick-backs made this an attractive case for the DOJ to pursue. The resulting DOJ investigation resulted in the confirmation of the original allegations made by the Serono whistleblowers. These allegations formed the basis of the DOJ's criminal charges under the FCA, as neither lipodystrophy or BCM wasting were medically accepted indications for which state Medicaid and federal healthcare programs could reimburse. The off-label promotion of Serostim formed the basis of civil complaints under the Federal Food, Drug, and Cosmetic Act (FDCA).

As part of a settlement agreement concluded in October 2005, Serono pleaded guilty to two felony counts: (i) conspiracy to introduce into interstate commerce an unapproved and adulterated medical device with an intent to defraud and mislead; and (ii) conspiracy to pay illegal remuneration to physicians to induce them to prescribe Serostim, for which payments were made by state Medicaid programs. Serono paid $137 million in criminal penalties for these violations. As part of the plea and the civil settlement agreement, Serono also agreed to pay $567 million in civil penalties based on its off-label marketing practices, and entered into a CIA with the OIG.

Although the settlement terms and the CIA offered Serono are based on the model set by the earlier Pfizer settlement of FCA and Anti-Kickback Statute violations related to its off-label promotion of Neurontin, they differ in substantial ways. They are similar in that both cases were initiated by disgruntled former employees under the proposition that the firm violated the FCA by its off-label promotional activity that resulted in reimbursement by a federal healthcare program, both resulted in stiff monetary penalties, and tough CIAs. The most glaring differences, however, lie in the enforcement tools used by the government against each firm resulting in the lop-sided civil versus criminal penalties of the

Serono settlement. In the Pfizer case, the government charged Pfizer with criminal misbranding violations under the FDCA, which were subsequently settled when Pfizer pleaded guilty and agreed to pay $430 million in criminal fines and civil penalties. In contrast, although the DOJ alleged that Serono had engaged in unlawful off-label marketing practices, Serono was never prosecuted for criminal misbranding violations under the FDCA. Moreover, although Serono faced $137 million in criminal penalties under the FDCA, the bulk of its monetary penalties were under a civil settlement agreement related to liabilities incurred due to payments made by state and federal healthcare programs for Serostim.

This emphasis on greater civil consequences of off-label marketing also resulted in a CIA far more burdensome than Pfizer's CIA in its application to off-label marketing practices. Although the Serono CIA, like the Pfizer CIA, requires the company to establish a comprehensive compliance program with an established Code of Conduct, written policies and procedures related to promotional activities, as well as rigorous training programs for off-label issues, the former includes caveats and restrictions on the funding and conduct of medical educational programs, as well as policies and procedures to ensure that financial incentives do not result in improper sales and marketing practices. The Serono CIA also specifically prohibits Serono from responding to requests for off-label information, unless those requests are made in writing, in order to more closely monitor such activity. The onerous terms of this CIA send an important message to industry that although the government may not criminally prosecute pharmaceutical firms for off-label promotional activities, the terms of any civil settlements will be financially burdensome and that unless they wish to be burdened with highly publicized CIAs under the watchful eye of the government, they should implement internal watchdog procedures against unlawful off-label marketing activities.

While the Serono case showcases governmental enforcement actions related to marketing activities, a recent "Corporate Warning Letter" from the FDA to Boston Scientific Corporation (Boston Scientific) dated January 25, 2006, indicates that the FDA can and will use hitherto rare, yet tough, enforcement actions against firms that are guilty of violating manufacturing processes. Together they provide a snapshot of government enforcement actions at both the downstream and upstream ends of the process of bringing a drug or medical device to market.

The FDA's Warning Letter to Boston Scientific represents a significant departure from normal Agency operation in compliance matters, especially as Warning Letters are typically issued to an individual manufacturing site or location, rather than to a corporate entity as a whole, and rarely originate from the upper echelons of the Agency. The Boston Scientific Warning Letter cited not one but three separate facilities, and was signed not only by the relevant FDA District Office Director (as is the usual practice), but also by the Director of the Office of Compliance in FDA's Center for Devices and Radiological Health (CDRH). The issuance of this Warning Letter was accompanied by a well-publicized press conference held by the FDA, signaling that when the Agency has serious manufacturing and quality concerns regarding a firm's operations, it will make such concerns well known.

As a general matter, the FDA does not issue Corporate Warning Letters. In fact, this is only the third time the CDRH has issued such a Warning Letter, according to FDA officials. However, not only is the rarity of such a Warning Letter surprising, but so are its contents. In the letter, the FDA requested a meeting between senior Boston Scientific officials and FDA New England District Office officials to address the issues raised in the letter. The FDA does not typically request such a meeting.

The reason for this significant departure in compliance action from the FDA may stem from the agency's concern that company-wide, systemic problems have occurred at Boston Scientific and that normal corrective actions have failed to adequately address and prevent the recurrence of such problems. It may also reflect a desire by the FDA to pre-emptively address with Boston Scientific the ongoing issues faced by Guidant, a firm Boston Scientific has recently agreed to acquire, and which also faces charges of serious regulatory compliance violations. The Warning Letter observations also illustrate the need for consistency in requirements and procedures at companies with multiple manufacturing facilities. For example, Boston Scientific had 23 different complaint handling systems in place, rather than one company-wide system, as a result of multiple acquisitions. Moreover, officials at one company site reportedly were unaware of a company recall initiated at another company site.

While Boston Scientific officials have committed to promptly resolving all FDA concerns, and have stated that the firm will be ready for a follow-up FDA inspection by June 2006 (a timeline that appears extremely aggressive), the firm's woes are not over yet. Depending on the outcome of that inspection, further FDA enforcement action may result.

Both of these enforcement actions by two different agencies emphasize the importance of vigilant oversight of manufacturing and marketing operations. The number of cases brought against pharmaceutical manufacturers for off-label promotional violations is expected to increase, and the advent of Medicare Part D coverage of prescription drugs will continue to expand the reach of these potential cases. The FDA's Corporate Warning Letter to Boston Scientific illustrates the Agency's intolerance for manufacturing discrepancies and deficiencies, thus requiring a significant expenditure of resources to correct. Emerging companies should invest resources early to develop corporate compliance systems addressing all aspects of the product life cycle and invest in quality manufacturing operations, to ensure they do not run afoul of government regulators.

Biography

Mr. Sanjay ("Jay") Sitlani is an attorney in the FDA and Patent Prosecution practice groups of Heller Ehrman White & McAuliffe LLP's Washington, D.C., office. Mr. Sitlani regularly advises drug, device, and biotechnology companies on matters involving the interpretation of federal laws and regulations, applicable state laws, and international regulations governing research and commercial development of biotechnology and pharmaceutical products. Mr. Sitlani has particular experience dealing with the regulation of pharmaceuticals, biologics, and devices by the FDA, and interpretation of the Hatch-Waxman Amendments to the Federal Food, Drug, and Cosmetic Act (FDCA) as they relate to market exclusivity strategies and domestic intellectual property issues. He is also experienced in prosecuting US and foreign patent applications for biotechnology products. Prior to entering the law, Mr. Sitlani worked as a research scientist in a biotechnology firm conducting stem cell research. He can be reached at (202) 912-2028, or jsitlani@hewm.com.

ADVANCED DELIVERY DEVICES

Key Considerations for Developing Combination Products

By: Christine M. Ford, MBA

Truly innovative products can improve the effectiveness of medical therapies, help to achieve efficiencies, and thus become part of sustainable solutions to healthcare challenges. In particular, there are significant opportunities for companies to take advantage of an emerging trend – the convergence of pharmaceuticals and medical devices in combination products. Often without the expertise to develop their own drugs, many medical device OEMs are looking for partnership and licensing opportunities with pharmaceutical companies or hiring pharma experts.

BENEFITS OF COMBINATION PRODUCTS

Combination products are composed of two or more regulated components – drugs, medical devices, or biologics, combined through physical or chemical means. These include drug-coated devices, drugs packaged with delivery devices in medical kits, and drugs and devices packaged separately but intended to be used together. Many such products bring together the power of advanced therapeutics with the precision dosing made possible by sophisticated delivery technologies.

According to Navigant Consulting, already valued at $5.4 billion in 2004, the global market for combination products is achieving annual growth of 10% to 14% percent a year. One of the most commercially successful combination products has been the drug-eluting stent. Combination products are also being marketed or developed for orthopedics (eg, protein-coated implants to encourage bone regeneration), cancer (eg, a tumor ablation system), infection control (surgical mesh with antibiotic coating), and diabetes care (integrated glucose meter and insulin pump).

The first transdermal patch for use in treating depression, Emsam (Figure 1), has just been approved by the Food and Drug Administration (FDA). At its lowest dosage, it can be used without the dietary restrictions needed for oral drugs in the same therapeutic class. Also recently approved by the FDA, an inhalant insulin product holds great promise for treating diabetes. Future combination product applications are expected to include implantable, closed-loop insulin pumps, steroid-eluting electrodes, or even novel "physical solutions," such as drug-coated surgical screws, catheters, sutures, and wire.

DEVELOPING A CONVERGENCE STRATEGY

Combining previously distinct product offerings – pharmaceuticals, medical devices, and diagnostics – can create openings in a crowded marketplace for truly exceptional products. But in developing a convergence strategy, it's important to follow certain best practices to meet the challenges of product development and regulatory approval.

First, it's crucial to have a clear understanding of the sales opportunities and potential value of combining previously distinct products or technologies. Are there new therapeutic processes or advancing technologies that set the stage for a combination product?

It's important to consider potential barriers to adoption of a combination product by healthcare providers, payers, and patients. Are these groups likely to be persuaded to overcome these barriers by the product's apparent benefits? Does a combination product represent a clear improvement over existing methods? Other strategic issues medical OEMs must consider are: how to find the right pharmaceutical or biotechnology partner, how to best structure deals, and what needs to be done to get through the FDA approval process.

A successful convergence strategy is likely to be an outgrowth of a company's core business. Developing combination products can, for example, help pharmaceutical manufacturers exploit the full potential of their drugs – and potentially extend the patient life cycles of their products. For medical device companies, combination products can be the wedge needed to expand their market share.

CONSULTING WITH USERS

In developing your products, it's crucial to consult with end users.

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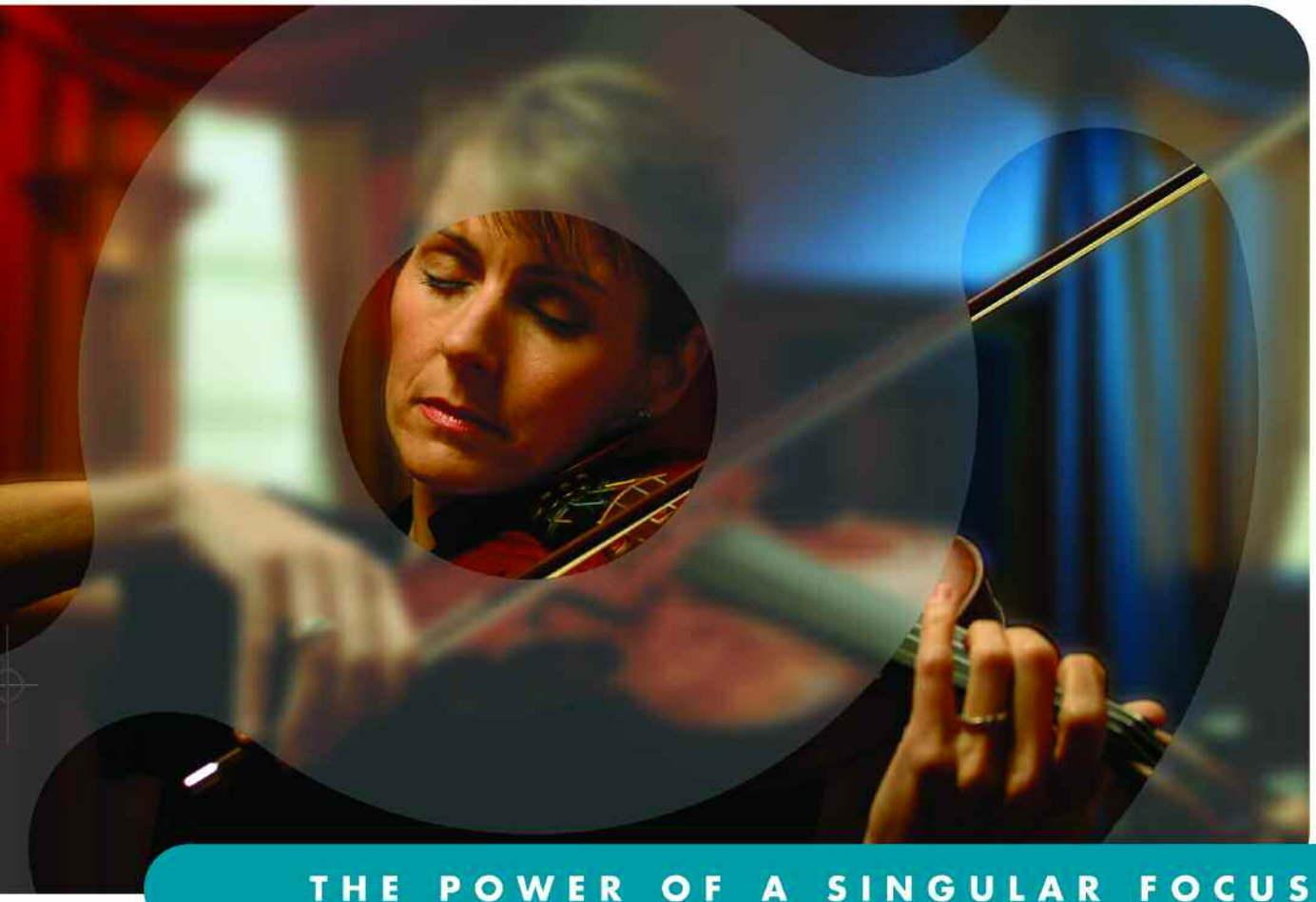

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Today's doctors face a bewildering range of choices, from novel clinical therapies to new methods of delivering care. At the same time, cost pressures and a more stringent reporting climate are placing constraints on their time and behavior. When developing and marketing combination products, it's important to consider how the tools might provide efficiencies through reduced labor or costs, or help to ensure patient safety.

Careful market research and testing among patients' healthcare professionals can point out flaws in current therapies and pinpoint areas ripe for innovation. Physician Advisory Boards and input from leading medical societies are a tremendous resource for innovation and feedback.

FIGURE 1

OUTSOURCING TO SPEED DEVELOPMENT

More and more firms are discovering the benefits of outsourcing to streamline product development, and not just in the traditional avenues of manufacturing and labor. For combination products, outside engineering and design firms can provide end-to-end solutions – from research and product development through to equipment design and testing –speeding time to market and potentially lowering costs.

Contrary to popular belief, outsourcing can actually help to preserve trade secrets. A third-party firm can provide stronger protection for a company's proprietary position than would internal development. By preserving anonymity – no one need know the companies you use – outsourcing can reduce the threat of competitors poaching valued employees. It's of course good practice to ask design firms to sign confidentiality agreements protecting intellectual property and providing competitive exclusivity.

Outsourcing can also help maintain project timelines and control costs, thus minimizing the effect of competing internal processes and keeping a team focused on a single goal. During the contracting process, it's important to hold third-party contractors to clear time and cost specifications and require periodic reports of progress. In addition, when selecting an outsourcing vendor for combination product development, it is critical that such firms understand the unique requirements of combining pharmaceutical, biologic, and/or device components as related to sterilization, lyophilization, and other unique manufacturing considerations.

FORGING PARTNERSHIPS AS A GROWTH STRATEGY

It's not likely that expertise in all aspects of pharmaceutical development, analytical skills, medical device engineering, quality control, and delivery systems will be housed in a single company. Strategic partnerships can bring together the multidisciplinary expertise needed for combination products, thus helping to bridge the divide between a good idea and a successful product.

Partner companies can offer fresh approaches and the benefits of experience to the development of combination products. For example, some partners might have foresight and market research about emerging opportunities, while others might have particular knowledge of legal and regulatory requirements.

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NAVIGATING FDA APPROVAL

Not surprisingly, there's a great deal of uncertainty about the regulation of combination products. Drugs, devices, and biological products each have their own types of FDA applications, good manufacturing practice regulations, and adverse event reporting requirements.

Wisely, the FDA has recognized that "one-size-fits-all" will not work for regulation of combination products, which are quite diverse in their design and application. Former FDA Commissioner Mark D McClellan, MD, PhD, said, "The FDA is prepared to meet the new opportunities of combination products by adapting its resources to address these new technologies." (see FDA.org) Since December 2002, the FDA's Office of Combination Products (OCP) has overseen combination product regulation. The actual regulatory responsibility lies in the FDA's drug, device, and biologics centers: the Center for Drug Evaluation and Research, the Center for Devices and Radiological Health, and the Center for Biologics Evaluation and Research.

To begin the process, applicants submit a Request for Designation to the OCP, which then has 60 days to assign the combination product to one or more of the centers. To ensure timely review, it's a good idea to consult with OCP staff about the appropriate regulatory pathway. Assignments are based on a determination of the "primary mode of action" (PMOA) of the product, defined by the FDA as "the single mode of action of a combination product that provides the most important therapeutic action." In cases where the primary mode of action is unclear, assignments are made based on determinations for similar products and relevant experience at the centers.

The OCP has not yet stipulated Good Manufacturing Practices (GMP) for combination products. For combination products produced as a single entity or packaged together, it has said that both Current Good Manufacturing Practice (cGMP) regulations for pharmaceuticals or drug products and Quality System (QS) regulations for medical devices are applicable. Biological product regulations also might apply.

Notably, the draft guidance states that it is generally not necessary for manufacturers of combination products to maintain separate manufacturing systems to ensure compliance. Recognizing that there is a great deal of overlap among the regulations, the FDA has said that compliance can generally be achieved by using a hybrid approach that draws upon both the cGMP and QS regulations.

Still, manufacturers should not assume that their usual processes will satisfy what are, after all, still-evolving requirements. To avoid surprises, it's recommended that manufacturers discuss their plans with the FDA at an early stage. Browsing the OCP website, which includes 140 examples of approved combination products, will provide a sense of the review processes thus far.

CAPITALIZING ON INNOVATION

Many experts predict that combination products will transform the medical industry and hold great promise for advancing patient care. It's likely that they will fuel greater competition as well as collaboration – as formerly separate players become competitors and/or partners. But in addition to presenting challenges in design, production, and approval processes, combination products offer exciting, unique opportunities. Even if they do not intend to enter this field for some time, manufacturers can benefit by creating a convergence plan and exploring the tools and partners needed to realize it. ◆

BIOGRAPHY

Ms. Christine M. Ford, is the Event Director, PharmaMedDevice™. Since joining Reed Exhibitions in 1991, she has been involved in a variety of conference and event management positions within a range of event portfolios, including technology, life sciences, entertainment, manufacturing, and real estate. Ms. Ford served as Reed Exhibitions' Director of Business Development from 2000-2005, working on a variety of launch and acquisition projects. Since 2004, she has focused the majority of her business development work within the life sciences and healthcare industries, including the PharmaMedDevice launch. Ms. Ford earned her MBA in Management and International Business from the University of Connecticut and her BS in Psychology from Fairfield University.

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Formulation Strategies for Poorly Soluble Drugs

By: Contributor Cindy H. Dubin

The pressing challenge pharmaceutical scientists have to face is the poor solubility of drug candidates. In a scenario where an increasing number of drug molecules are generated, the impact of biopharmaceutical properties, including solubility, on drug development tend to be underestimated. Nonetheless, water insolubility can hamper or completely halt new drug development.

As a matter of fact, estimates indicate that poorly soluble compounds represent about 60% of compounds in development and many major marketed drugs. At last year's *Drug Delivery Technologies & Deal-Making Summit* (September 2005), Gesine Hildebrand, PhD, Modified Drug Release, Schering AG, pointed out some interesting statistics in her presentation, *Poorly Soluble Drugs – Meeting the Formulation Challenge*, including:

- 1/10 of marketed drugs have solubility problems;
- more than 1/3 of drugs in the pipeline are poorly soluble; and
- nearly 2/3 of drugs coming directly from synthesis have low solubility (<0.1 mg/ML).

Solubility issues complicating the delivery of new drugs also affect the delivery of many existing drugs. What most influences the absorption process? According to Dr. Hildebrand, the top factors are:

- release rate from the delivery system;
- drug degredation within the GI tract, GI content, pH, enzymes, and amphiphilic bile secretions;
- delivery system transit time through the GI tract;
- first-pass metabolism and potential exsorption into the GI tract; and
- dose to solubility (D/S) ratio.

FORMULATION TECHNOLOGIES FOR POORLY SOLUBLE COMPOUNDS

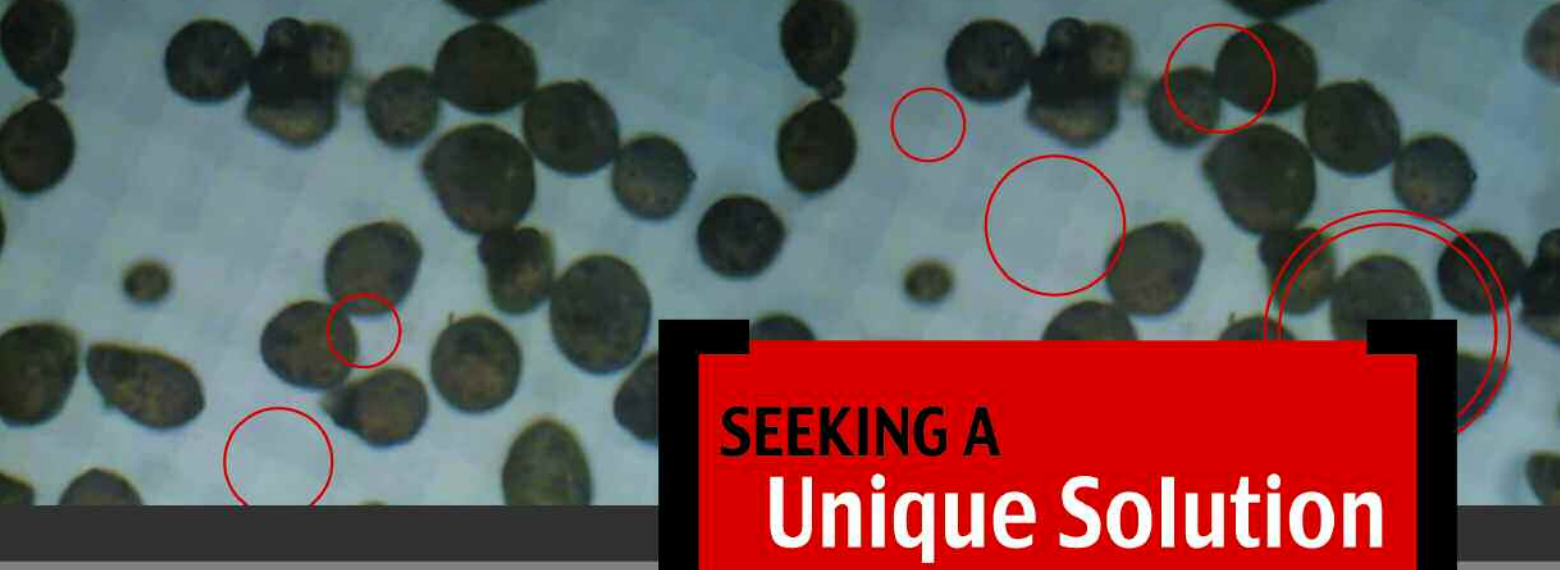
Fortunately, preclinical and formulation scientists suggest that there is indeed a light at the end of the solubility tunnel in the form of a variety of technologies meant to improve solubility. OctoPlus of The Netherlands offers several specialized technologies to improve solubility and bioavailability of compounds, such as liposomes, mixed micells, and the excipient inulin.

Liposomes: Low-soluble compounds can be solubilized in the hydrophobic space of mixed micells and liposomes. The liposome family consists of vesicular structures that can be used as carriers for drugs and antigens. They consist of bilayers composed of (phospho)lipids. According to the company, these vesicular structures vary in size, bilayer rigidity, bilayer geometry, and charge. They can be as small as 30 nm and as large as 30 μm. By selecting the proper lipid(s), the bilayer can be neutral or positively or negatively charged. Bilayer rigidity depends on the lipid choice as well and plays a critical role in drug/antigen release kinetics and stability on storage. Depending on their physico-chemical characteristics, liposomes can successfully alter the disposition and improve the therapeutic potential of a drug. Benefits of liposomes include the following:

- they are excellent solubilizers of lipophilic drugs, allowing intravenous administration of these often poorly water soluble compounds;
- can enhance the immune response against antigens in vaccines;
- can be used in dermatological preparations to enhance skin penetration;
- can be used for slow release of the associated drug after intramuscular or subcutaneous injection;
- can be used for passive targeting of the associated compounds to macrophages, to tumor tissue or inflammation sites;
- homing devices can be attached to liposomes for active targeting to diseased sites; and
- cationic liposomal structures are successfully being used as synthetic gene transfection systems.

Mixed Micells: Mixed micells do not have a double layer, but do have a hydrophobic core in which low-soluble compounds can dissolve. Also for this group of particles, different compounds can be chosen to increase solubilization. However, compared to liposomes, mixed micells offer a little less flexibility in the choice of their physico-chemical characteristics.

Inulin Glasses: Inulin is an excipient meant to increase the solubility of lipophilic compounds. Inulin is a naturally occurring fructose polymer. The compound has a history of safe parenteral use in medicine as the gold standard by which to measure the glomerular filtration rate. Furthermore, the compound has obtained GRAS status (Generally Recognized As Safe) from regulatory authorities, facilitating use in oral applications. Mixing an inulin solution with a drug solution, followed by freeze-drying under appropriate conditions



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results in the formation of a sugar glass. Uniquely for inulin, the dissolution profile of the lipophilic compound incorporated is closely related to the dissolution of this sugar glass. This leads to a strongly enhanced, reliable dissolution for the low-soluble active component. The sugar glasses that emerge from this process also protect the compound against physical and chemical degradation, thereby increasing stability. The inulin formulation technology is suitable for oral and pulmonary applications.

Focused on parenteral administration, researchers at the University of Illinois at Chicago have discovered and developed a biocompatible drug delivery platform with broad applications to the delivery and stability challenges posed by water-insoluble drugs, proteins, peptides, and vaccines. Daniel F. Marselle, Director, Pharmacy Intellectual Property, says liposomes, phospholipid micelles, and micelle-containing liposomes are modified to include a water-soluble polymer, such as polyethylene glycol, offering reticuloendothelial system (RES) protection and increased water solubility, which is advantageious for intravenious administration of these products.

NANOTECH-ENABLED DRUG DELIVERY SYSTEMS

While some still consider nanotechnology to be "futuristic," research firm NanoMarkets predicts that nanotechnology-enabled drug delivery systems will be one of the first true nanomedicine markets to evolve and will generate sizable revenues.

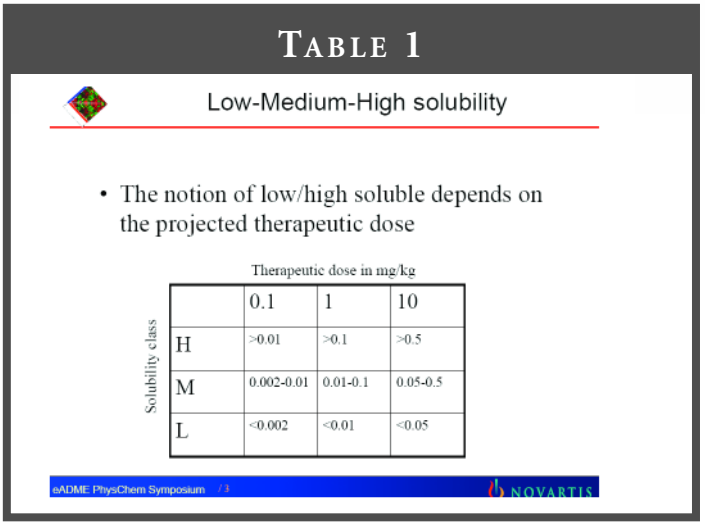
A white paper from the company states that "these nano-enabled drug delivery systems promise to increase the bioavailability of drugs and reduce the likelihood of toxicity," the paper states.

Johnson & Johnson is at the forefront of using nano-enabled drug delivery, and according to NanoMarkets, nanotechnology is likely to have an impact at J&J. Injectable drug delivery systems, which generally involve some discomfort for patients, are one area likely to benefit from nanotech. Johnson & Johnson is conducting a Phase III study of a long-acting formulation of its schizophrenia drug paliperidone palmitate using Elan's NanoCrystal technology. The technology transforms drugs into nanometer-size particles that can be used to create tablets, capsules, liquids, and powders. NanoCrystal is intended to improve paliperidone palmitate solubility and could result in J&J being granted extended patent life on the compound.

SOFTWARE

Exhaustive drug solubility screening early in the development process has become an important focus for pharmaceutical scientists. Low solubility can hamper a drug's bioavailability and make ADME assays more difficult. Solubility assays are also vital for development scientists who need to select amongst salt or crystalline forms, evaluate formulation excipients, and determine minimum absorbable dose. The new ReactArray ST automated

TABLE 1



equilibrium solubility testing workstation enables fast, convenient, and efficient gathering of critical data under completely controlled conditions. Developed through a collaboration between Anachem and chemists within the pharmaceutical industry, ReactArray ST, based on the ReactArray 215SW platform, is fitted with a 10-position Reactivate rack with individual temperature (-30°C to 150°C) and stirring control.

A design study vessel includes a spring-loaded filter. During sampling, the workstation probe presses the test device down into the slurry at equilibrium; the probe then takes a quantitative filtered sample for subsequent HPLC analysis. The test device has been shown to deliver data across a range of solvents and temperatures. ReactArray ST is calibrated so that concentrations can be plotted as a bar graph (single temperature studies) or as a solubility curve (multiple temperature studies).

Software has also proven effective in determining the solubility of drug molecules in polymers for transdermal drug delivery systems. Formulators typically develop a patch to have a drug loading above the solubility limit in order to obtain zero-order release kinetics. To achieve this, they need to choose a polymer with optimum drug solubility. This usually requires time-consuming measurements of drug transport (flux). Flux depends on both the solubility and the diffusion constant of the drug in the particular matrix.

National's Drug-In-Polymer Solubility Calculator requires that a user input the drug octanol-water partition coefficient and the drug-water solubility. Results are instantaneous. The tool can aid patch developers in selecting the best polymer for a particular drug delivery application.

Then there's Advanced Chemistry Development's solubility database, which can be used to filter libraries of compounds for a specified solubility range, and to create chemical compounds with specified solubilities at a given pH. According to Daria Jouravleva of ACD, knowledge of a compound's aqueous solubility can lead to an understanding of its pharmacokinetics, as well as an appropriate

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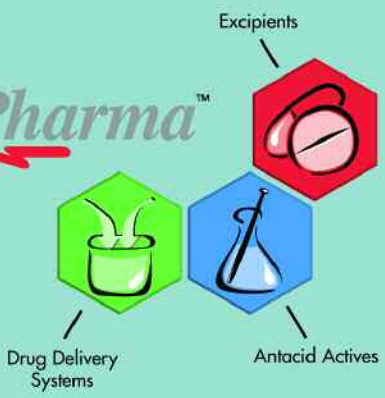

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means of formulation.

"Solubility of organic compounds in water has become increasingly important for studies of oral absorption of pharmaceuticals and of the toxicity of chemical compounds," says Dr. Jouravleva.

Predicting aqueous solubility with ACD/Solubility DB allows one to anticipate the characteristics of compounds before synthesis or before a sample is acquired. The benefits: Chemists can avoid making insoluble compounds; specialists who acquire screening compounds on behalf of their companies can avoid buying insoluble compounds; screeners can adjust the target concentration to account for low solubility, or just choose to avoid screening low solubility compounds; and formulators can anticipate the solubility profile of drugs before doing confirmation experiments.

In short, says Dr. Jouravleva, accurate prediction of aqueous solubility can focus drug discovery research on appropriate compounds and shunt effort away from active compounds with very poor probability of in vivo success.

DOSING & SOLUBILITY RATIO

From a biopharmaceutical standpoint, the determination of drug solubility, with respect to its anticipated dose, is the most important parameter that needs to be determined. Solubility is important because the ratio of the anticipated dose of a given drug to its solubility, together with the dissolution rate, determine the fraction of the dose available for absorption. "The notion of low/high soluble depends on the projected therapeutic dose (Table 1)," suggests Bernard Faller, Novartis Institutes for Biomedical Resarch.

Since gastric and intestinal fluids are a complex mixture of natural surfactants, salts, and buffers, it is also important to determine the effect of pH, salts, and surfactants on a drug's solubility. TSRL Inc. of Ann Arbor, Michigan made such a determination for a client that had concerns about pharmacokinetic data from a variety of formulations of its lead compound. The drug was poorly soluble, and was being evaluated in a suspension formulation. TSRL was asked to determine solubility and permeability of the bulk drug and of the drug in suspension.

"We looked at drug solubility in a variety of media, and over a range of pH and surfactants," says a TSRL company spokesperson. "From the permeability and solubility data, it was clear that drug absorption for this drug was solubility-limited. Interestingly, one of the formulations provided to us showed relatively high solubility when compared with the other formulations or bulk drug. It became apparent that some of the dispersants contained within that suspension formulation were responsible, in large part, for the increased solubility of the drug. Since this same formulation showed the highest Cmax and AUC in the pharmacokinetic experiments, we provided our client with a mechanistic explanation of the *in vivo* data."

TSRL has developed two drug solubilization technologies for insoluble or poorly soluble drugs. The first is a water-soluble pharmaceutical coating based on lecithin and gelatin termed Hydrophilic Solubilization Technology or HST that increases the dissolution rate of poorly soluble drugs. This technology improves dissolution of poorly soluble compounds by preventing particles from aggregating together once exposed to an aqueous environment and by increasing the solubility through micellization. Both of these processes result in improved oral bioavailability.

The second technology is a microemulsion drug delivery system termed Lipophilic Solubilization Technology or LST that improves the bioavailability of water-insoluble drugs over other microemulsion systems. This technology consists of a lipid/solvent drug reservoir with a proprietary combination of surfactant(s) and co-surfactant(s) that forms a microemulsion when in contact with an aqueous environment. The emulsion-solubilized drug is then further solubilized in the small intestine and absorbed, resulting in improved oral bioavailability.

SUMMARY

Fortunately, preclinical and formulation scientists suggest that there is indeed a light at the end of the solubility tunnel in the form of a variety of technologies meant to improve solubility. As drug delivery experts continue to develop drugs that are safer, more effective, and more convenient for patients, solubility remains at the forefront of their formulation efforts. Companies must continue to optimize the effect of drugs on the body through technologies that measure and determine rates of solubility as well as aim to overcome the challenges of low-soluble drugs. ♦

BIOGRAPHY

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

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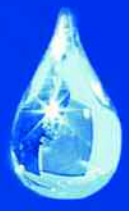

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NANOBIOTECHNOLOGY

Nanobiotechnology: Delivering Revenue, Exciting Promise for the Future

By: Jason McKinnie, Research Analyst, Frost & Sullivan

INTRODUCTION

The pharmaceutical nanobiotechnology market is now measured in billions due to the continued success of launched reformulations utilizing sophisticated nanotechnology and first-in-class products that encompass nanoparticles. New prescription products or formulations drove the market to over $1.5 billion in 2005, primarily driven by the reformulated fenofibrate, TriCor from Abbott Laboratories, and the first approved nanobiotechnology drug, Abraxane, from Abraxis BioScience. The market continues to grow as academic institutions, private sector companies, and government agencies invest heavily into nanobiotechnology for creation of novel products, delivery systems, and methods of manufacturing for better solubility.

NANOBIOTECHNOLOGY: A BRIEF BACKGROUND

Nanobiotechnology generally refers to the delivery or manufacturing of novel or reformulated drugs utilizing nanotechnology or small particles. Manufacturing techniques vary widely between companies in this space but most use some sort of technology to create nanocrystals or nanoparticles that result in a reduced drug particle size, creating more surface area. Processes like these allow for poorly soluble drugs to be delivered more efficiently into the body, potentially reducing dosages and side-effect profiles.

CURRENT & PROMISING APPLICATIONS

Elan Corporation continues to be the leader in nanobiotechnology with four marketed products utilizing its proprietary NanoCrystal technology. The company's latest reformulation was for the third-generation fenofibrate (TriCor) from Abbott Laboratories. Due to the formulation advancement, TriCor is no longer required to be taken with food, allowing dosing flexibility for patients as well as lowering the overall dose. NanoCrystal technology encompasses a wet-milling technique that reduces the size of drug particles to less than a 1000 nanometers. The reduced size allows for a substantial increase in surface area, leading to better solubility.

Improving drug delivery systems for existing products or incorporating drug delivery in drug development is an important concept for many in the pharmaceutical industry. The inability to deliver a drug to the proper target leads to side effects, inefficacy, and unnecessarily high dosages of the drug. Improving solubility through nanotechnology manufacturing eliminates some of the problems associated with delivery, but utilizing nanoparticles for the drug itself can provide even more dramatic effect. Abraxane from Abraxis BioScience was the first drug incorporating this technology approved by the FDA. Since its market launch in February 2005, it has generated $166 million in 14 months and garnered a share in the breast cancer treatment market. Abraxis BioScience's technology, nanoparticle albumin bound (nab), uses albumin particles to surround paclitaxel, creating a total particle size of approximately 130 nanometers. This small particle paclitaxel eliminates the need for toxic solvents, such as Cremaphor, and allows for an increased dosage to better treat cancer patients with less side effects.

The importance of the nab technology from Abraxis BioScience and overall nanobiotechnology was affirmed in April of 2006. At the

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"Nanobiotechnology continues to be one of the most promising technologies in pharmaceuticals. While still in its formative stages, the technology has already improved drug delivery and manufacturing processes to create a market over $1.5 billion in product revenue."

annual meeting of the American Association of Cancer Research, the company presented positive data on the use of nab technology with other drugs, including docetaxel. Other research also explained why tumor cells preferentially absorb albumin, giving more credence to the ability of nab technology to target tumor cells. The announcement of co-promotion rights of Abraxane between Abraxis BioScience and AstraZeneca also occurred in April. The attention of big pharma shows nanobiotechnology is a legitimate form of drug delivery and has promise for the future in regard to providing better patient care and generating revenues.

Dendrimers continue to be an important compound in the development of nanobiotechnology therapeutics for their immense flexibility. A dendrimer consists of three basic parts: a core molecule, branching molecules, and surface molecules. The dendrimer's size can be easily modified through increasing the amount of branching molecules. The spherical shape of dendrimers lends itself to a large surface area, and a simple linear increase of branching molecules leads to an exponential increase of surface molecules. The surface molecules can be modified to express a variety of different properties, including hydrophilic, hydrophobic, or electrophilic. In addition, the surface molecule can be modified to bind with a receptor or small molecule. Dendrimers can also be used to transport poorly soluble drugs, such as chemotherapy agents, by encapsulating them within the branch molecules. A large dendrimer, on the order of 10 generations of branching molecules, forms a rigid sphere that does not easily allow particles in or out due to the forces of the surface molecules. This carrier is potentially very convenient for drugs that require toxic solvents, such as paclitaxel, because the dendrimer can be made soluble through manipulation of the surface molecules and administered with simple saline.

The Michigan Nanotechnology Institute for Medicine and Biological Sciences (M-NIMBS) is also a leader in the field of dendrimer-based therapeutics and creating nanodevices to perform relevant tasks, such as delivering therapeutics or imaging agents for diagnosis. M-NIMBS uses dendrimers as the backbone for all their nanodevices and has created an extensive catalog of dendrimers encompassing the different functional groups they want. Tecto-dendrimers are a more complex nanodevice that includes multiple dendrimers with functional groups, such as an imaging molecule, diseased cell recognition molecule, and therapeutic molecule. They are also working on a dendrimer that can show apoptosis occurred through an imaging molecule. The combination of all these functionalities is expected to create a very powerful nanodevice that is capable of finding the diseased cell, delivering a therapeutic, and reporting success of cell death.

M-NIMBS is working on a multitude of specific nanodevice projects for cancer therapeutics. Folic acid receptor is commonly overexpressed in ovarian and head and neck cancer and as a result, they are working on developing a dendrimer that can recognize that receptor. The group is also working on a dendrimer that binds to the PSMA associated with prostate cancer. To date, these projects have not moved into human clinical testing but show promise for targeting drug delivery to specific cancers while limiting side effects.

Nanoemulsions are another key source of research in nanobiotechnology and specifically M-NIMBS. Composed of non-toxic lipid drops, nanoemulsions are relatively easy to manufacture and have shown great promise in killing bacteria, enveloped viruses, and other

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pathogens by disrupting the surface of the organism. In addition to their antimicrobial properties, they appear safe to human skin and mucous membranes to the point where the FDA allowed a topical herpes nanoemulsion treatment to proceed to Phase II clinical trials, bypassing the safety of Phase I trials. Nanoemulsions are being developed for the treatment and prevention of microbial infections as well as a system for delivering vaccines. Using a nanoemulsion to envelope a virus disrupts its membrane, rendering it inactive while still preserving it as an excellent template for immunization. Animal studies showed a nanoemulsion with influenza virus created an intense immune response that provided immunity from subsequent infections. This method is currently being tested in development of smallpox, anthrax, and hepatits B vaccines.

Starpharma and its partially owned partner company Dentritic NanoTechnologies are leaders in the development of nanobiotechnology for therapeutic use. Their lead product candidate, VivaGel, was granted FDA fast-track status for its use in prevention of HIV and herpes viral infections. The topically applied gel works by binding to the GP120 protein on the surface of HIV, inhibiting its ability to bind to T-cells and infect individuals. The companies hope the product can enter the market in 2008 and capitalize on a market that has no comparable product.

Other companies are also seeking to develop improved vaccine delivery through nanobiotechnology. BioSante Pharmaceuticals has developed a calcium phosphate (CAP) nanoparticle delivery system, called BioVant, to improve safety and efficacy of vaccine delivery. The CAP nanoparticles are derived from transgenic milk proteins and provide a uniform particle for coating of viral antigens. The nanoparticle also contains a substantial volume for internal loading of viral antigen. Storage of these particles is also improved, adding long-term storage as an option without suffering changes in size, pH, or surface morphology. Animal studies have shown their BioVant delivery improves immune response with 100 times less vaccine antigen, which allows for less reaction and infrequent complications. A Phase I study in humans showed no difference between the CAP nanoparticle and placebo; the next step for the company is testing the vaccine adjuvant in humans. The company has signed numerous development deals with government and businesses for use of their CAP nanoparticles in development for vaccine, allergy, anesthetic, and cosmetic products.

SUMMARY

Nanobiotechnology continues to be one of the most promising technologies in pharmaceuticals. While still in its formative stages, the technology has already improved drug delivery and manufacturing processes to create a market over $1.5 billion in product revenue. This trend is expected to continue as companies like BioSante Pharmaceuticals and StarPharma, as well as the academic endeavors of M-NIMBS, push the envelope of knowledge at the nanoscale level and develop pharmaceuticals that improve patients' lives.

BIOGRAPHY

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

BUSINESS MODELS

The Transformation From Drug Delivery to Specialty Pharma Company

By: Jon D. Meyer, MSc, MBA

INTRODUCTION

Some drug delivery companies are undergoing a change in their business model paradigm, making the conscious decision to transform themselves from "traditional" drug delivery companies to commercial developers/marketers of specialty products – specialty pharmaceutical companies. The risks associated with product commercialization are greater than those associated with traditional drug delivery development and licensing; however, so are the resultant rewards. While an arduous proposition, a well-conceived, actionable strategy can help a drug delivery company successfully navigate the transformation process.

SO WHAT MAKES A SPECIALTY PHARMACEUTICAL COMPANY?

The definition of a specialty pharmaceutical company varies greatly. Some of the generally accepted working descriptions include the following:[1]

- Companies that are not Big Pharma or Big Biotech;
- Companies focused on drug development and marketing to a select group of physicians;
- Companies reformulating existing drugs for target niche markets;
- Companies that in-license/acquire and commercialize products unattractive to the original developer;
- Companies that combine products from approved molecules and established delivery systems; and
- Companies that in-license, develop, and market late-stage clinical candidates.

While the definition of a specialty pharmaceutical company is diverse, there are common themes. Specialty pharmaceutical companies develop/commercialize molecular entities, reducing the time, cost, and risk compared to fully integrated pharmaceutical or biopharmaceutical companies.

WHY MAKE THE TRANSFORMATION?

Traditionally, drug delivery companies have adopted a business structure not unlike that of "benchmark" drug delivery firms, including Alza and Elan. To oversimplify the model, a drug delivery technology or system is first developed or licensed (which includes varying degrees of supporting preclinical/clinical development), followed by strategic licensing to Big Pharma partners. With these first partnerships come up-front licensing fees and subsequent, success-based milestone payments. If the drug delivery company is lucky, a small royalty rate may be negotiated. Variations on this theme are carried out with the same platform technology or other delivery systems. The result is a portfolio of licensing agreements and up-font licensing payments, followed by success-based milestones. While this proven strategy yields a viable business model with limited risk, for cash-hungry and/or nascent drug delivery companies, revenue streams and shareholder value remain limited. In exchange for much needed cash and a lower level of risk, drug delivery companies sacrifice lucrative back-end product revenues/royalty payments.

On the other side of the equation, specialty pharmaceutical companies face significantly increased risk, with the potential for more favorable economics. As seen in Figure 1, companies commercializing specialty branded drugs typically retain up to 10% of drug revenue in a licensing deal occurring as early as the discovery/formulation stage of development.[2] As the specialty pharma company retains the product further through development, the percent revenue capture climbs. Not surprisingly, companies that are able to develop their own sales force and market their products fare even better. Often, these companies can retain up to 65% of revenues through strategic targeting of niche markets and high-prescribing/specialty physicians, while entering into strategic co-promotion agreements for large/primary care

markets. Simply stated, in exchange for increased risk associated with drug development/commercialization, specialty pharma companies profit from larger future revenue streams, and corresponding company valuations.

THE TRANSFORMATION PROCESS

The transformation from drug delivery to specialty pharma company is a complex process. Transformation presents strategic, financial, and tactical challenges that must be researched, planned for, managed, and overcome. Additionally, the ramifications associated with unsuccessful transformation need also be considered. Strategic transformation questions that must be addressed by the drug delivery company include:

- How can a drug delivery company evaluate whether transformation makes sense or not?
- What should a drug delivery company do to prepare for the transformation?
- How can a drug delivery company execute the actual transformation?
- How can the company track and evaluate progress in the transformation process?
- What can be done if circumstances change?

Once it is determined that consideration should be given to the transformation process, the first objective is to develop a strategy and plan for evaluating and, if analysis deems favorable, executing the process. While every company is different and presents its own unique set of circumstances, the transformation process can be simplified by the the process illustrated in Figure 2.

A thoroughly planned and executed strategy requires the drug delivery company to *Evaluate* its current position and ability to undergo successful transformation. Steps include reviewing the current strategic plan, conducting internal assessments, evaluating pros and cons and risks and rewards, and finally making a go/no-go decision. With a "go" decision, a company should *Prepare* for the transformation by building a robust plan that includes clearly defined goals and actionable strategies. With a plan in place, the company can *Execute* the transformation process, ultimately resulting in late-stage out-licensing/commercialization of a product and capture of a revenue stream. Finally, the company should *Track* progress, *re-Evaluate* its plan, and establish a mechanism to drive corrective action should it be warranted.

Evaluate

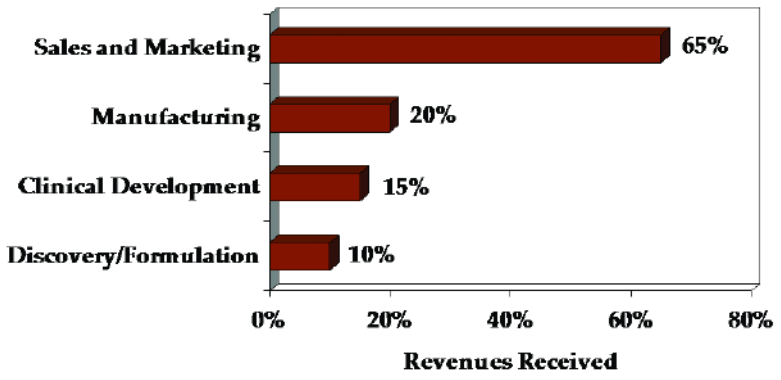
The first step in the transformation process is to evaluate the company's ability to successfully execute the transformation process. Critical questions should include:

- What is the company's current business model and strategic plan?
- Is the company currently on track with its existing strategic plan?
- How does the transformation to a specialty pharmaceutical company align with the plan? Are adjustments needed and should they be made?

With a thorough understanding of its business model and strategic plan, the drug delivery company can determine its strengths and which assets can be leveraged for the transformation. Assets can include capital, drug delivery platforms, intellectual property/technologies, human capital, and other strategic resources. A careful inventory should be prepared to ensure opportunities are not overlooked. Along with assets, the company should also review and understand its own capabilities. This can be accomplished through discussions with key internal stakeholders. Companies can also evaluate past efforts, resultant outcomes, and perform gap analyses to identify potential deficiencies and weaknesses, with the ultimate goal of making a

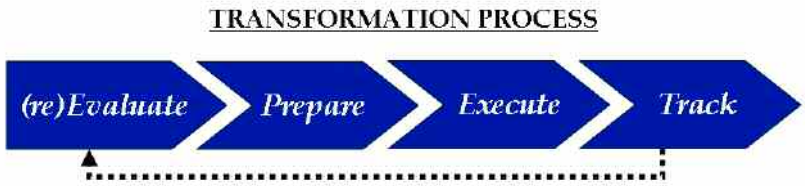
FIGURE 1

SPECIALTY BRANDED REVENUE CAPTURE



Specialty Branded Drug Revenue Capture

FIGURE 2



The Transformation Process

"realistic" assessment of true capabilities. The company then needs to identify what type and level of growth is expected internally and what other options are available. Questions the company should consider include:

- What is the 5-year plan?
- Are there expectations set by internal management or the Board of Directors?
- What are the expectations of the shareholders?
- What expectations does the street have for the company?

With growth expectations understood, the company can identify and consider the pros and cons associated with transformation. It is important to consider whether the pros really do outweigh the cons, if there are risks not fully understood, how many there are, and their potential impact on the attractiveness of transformation. This is typically a difficult process, as it requires the drug delivery company to evaluate differing scenarios, including the "worst-case" situation. It also requires the company to delineate which risks are internal versus external, and which the company believes it can successfully mitigate with careful analysis and planning. Finally, the process requires the company to ascertain its own risk/reward level and to compare it with the risk associated with transformation. If done correctly, the step will force the company to ask itself the tough questions and consider if transformation is truly possible. If from this process all signs point in the right direction, a "go" decision can be made.

Prepare

The next step in the process is to thoroughly *Prepare* for the transformation. First, the company needs to build a comprehensive transformation plan. This strategic plan is arguably the most critical component of the transformation process and the place where proper diligence and expertise can set the stage for success. The plan is the "roadmap" the company will follow as it undergoes the transformation and includes the goals and objectives of the transformation process, strategies, and tactics used to achieve those goals, a timeline for the process, key personnel, financial requirements/financing, and contingency plans.

Critical to the success of the transformation plan (and the company's transformation) are clearly defined goals and objectives. The goals should state the overall intent of transformation, while the objectives should detail specific strategies the company will use to execute the transformation. The transformation plan should also be actionable in that it should include the actual strategies, methods, and tactics the company will employ. Also, key stakeholders should be identified for each task so as to ensure individuals involved in the transformation will take ownership of their responsibilities.

The transformation plan should also contain a thorough analysis of the first product candidate, its proposed/planned life cycle, its market and financial opportunity, and the competitive environment, among other factors. The transformation plan should also project beyond the first product and identify a portfolio strategy with near, mid, and long-term candidates that will be required for the ultimate success of the company. With these components assembled, internal resources can then be gathered, including internal management, key product/brand teams, as well as any other external support that will be needed, such as external advisors, partnering models, or information.

Should additional capital be needed for a product or partnership, financing options need to be evaluated. Financial models can be developed to address multiple parties and evaluate multiple deal scenarios, including licensing/upfront payments, revenues, and royalties. Through this analysis process, the company can solidify its position and set its maximum/minimum boundaries for transformation.

Execute

With a robust transformation plan in place, the drug delivery company must then *Execute* its transformation plan. The first step should be to develop any partnering materials that will be needed for the process and to refine the pitch. With materials prepared, candidate product or financing partners can be approached and products/financing deal terms discussed. At this point, the time and effort spent initially preparing for transformation will start to pay off. With a

thorough understanding of potential deal parameters, the drug delivery company is in the best position to negotiate the best deal and terms. Also, maximum boundaries will be fully understood, further mitigating the repercussions of a "bad deal." At this point, external resources and/or team members can also be brought in to complete and complement the existing team. Tactical plans can also be finalized and reviewed with all key stakeholders. It is a good time to review contingency plans to ensure they are still appropriate for the existing circumstances surrounding transformation. This can be followed downstream by further execution of the initial product commercialization strategy, product launch, and portfolio expansion.

Track

After successfully evaluating, preparing for, and initiating the transformation process, the drug delivery company must *Track* its overall progress. A performance tracking system should be implemented to monitor and evaluate key performance indicators (KPIs) for both the company and the product(s). The system should delineate KPIs related to the transformation objectives and strategies and should report on current status. The process will allow the company to check alignment with transformation goals and consider the company's ability to maintain its forward momentum. Finally, the tracking system will help the company identify areas of difficulty and take corrective action where needed.

(re)Evaluate

It is important to remember that transformation is an iterative process. The company should not be afraid to periodically *re-Evaluate* and challenge the current strategic plan, making course adjustments as necessary. Some of the questions that should be addressed include:

- Have business models changed or are there other models that make more sense?
- Does the strategy align with our core business strategies and still make sense?
- Is the company executing according to plan?
- Does the company need to revise its plan or take corrective action?
- How will a shift in direction impact company motivation?

CRITICAL SUCCESS FACTORS

The transformation from drug delivery to specialty pharmaceutical company is an arduous process. It is beset with pitfalls and challenges the drug delivery company must consider, plan for, address, and ultimately overcome to become successful. While some companies may be able to carry out the transformation with minimal assistance, there are several factors, that when considered collectively, can help ensure success. First, it is vital to have a robust strategic plan that sets clear and obtainable goals and objectives. Direction in the plan needs to be actionable, and the plan should also offer simplicity and flexibility – circumstances can change and so should your plan. Another factor for success is a financing strategy focused on long-term growth. Avoid settling for a bad deal and sacrificing all back-end revenues for up-front licensing or milestone payments. A portfolio approach to product development and commercialization is another factor for success. The approach provides speed to market with expansion potential, risk mitigation, and potentially a continued stream of revenues. A robust and comprehensive patent defense strategy can protect and maintain your investments when challenged by the competition. Finally, do your homework – it is easy to "short-cut" vital product, market, and competitor and/or deal structure/terms research and analysis. Careful attention to these factors will ensure the greatest potential for transformation success.

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BIOGRAPHY

Jon D. Meyer is an Associate Director in the Life Science group at Navigant Consulting. His experience spans pharmaceutical, biotechnology, and drug delivery companies across all stages of the product life cycle. His drug delivery experience includes oral/buccal, inhalable, implantable, transdermal, and injectable drug delivery systems/products in support of business development, new product planning, commercialization, and brand management activities. His methodological experience includes strategic planning, licensing, product commercialization support, market analytics, primary interviewing/focus group moderation, and competitive benchmarking. Prior to his experience at Navigant Consulting, Mr. Meyer was a Research Associate with Roche Bioscience. Mr. Meyer holds advanced degrees in biomedical science and business administration.

Clinical Studies of Terbutaline Controlled-Release Formulation Prepared Using EUDRAMODE™

By: Hema Ravishankar, PhD, MPharm; Jayanthi Iyer-Chavan, PhD, MSc; Preeti Patil, MPharm; Ashwini Samel, MPharm; and Gerhard Renner, PhD

ABSTRACT

The development and application of EUDRAMODE™ technology to alter the release pattern in order to achieve desired profiles was described in our previous publication.[1] The aim of this study was to evaluate a terbutaline controlled-release formulation prepared using EUDRAMODE™ technology and compare the pharmacokinetics parameters with Bricanyl Duriles® (reference controlled release formulation). The study was designed as a randomized three-treatment, three-period, three-sequence, single-dose, crossover study of the in-house controlled-release formulation, Bricanyl Duriles and Terbul® tablet (reference immediate-release formulation) in 18 healthy, adult, human volunteers under fasting conditions. Pharmacokinetic parameters, such as C_{max}, $AUC_{0\rightarrow t}$, $AUC_{0\infty t}$, T_{max}, K_{el}, and $t_{1/2}$, were determined by using the WinNonlin Ent Version 4.1 pharmacokinetic data analysis software program. It was concluded from the results that the in-house controlled-release formulation and Bricanyl Duriles showed similar pharmacokinetic parameters. A C_{max} of 5.318 and 5.193 ng/ml was reached at 5.00 and 4.75 hours (T_{max}), respectively. Terbul tablets being an immediate-release formulation reached a C_{max} of 4.516 ng/ml at 2.75 hours (T_{max}). An IVIVC was obtained that could be considered biorelevant and serve as a development tool for further dissolution or formulation refinement.

INTRODUCTION

Terbutaline sulphate, a β1 agonist, is widely used for the therapeutic management of chronic conditions of asthma and nocturnal asthma in particular. For the prophylactic management of asthma particularly nocturnal asthma, a long-acting formulation would be of benefit.[2-4]

Controlled-release drug delivery systems have the potential to provide continuous drug release in which drug levels of blood would remain constant throughout the delivery period. A number of design options are available for the preparation of controlled-release delivery systems, such as osmotically controlled drug delivery systems, hydrogels, polymer-based matrix systems, reservoir-type systems, micromatrix beads used in intestinal protective drug absorption systems, but the challenge lies in developing systems that would be flexible to enable drug delivery based on the therapeutic requirement.[5-12]

EUDRAMODE™, invented by Degussa, is an alternative multiunit oral technology that involves modulation of drug release by ionic interactions. The system consists of EUDRAGIT® NE-coated salt cores layered with drug and further coated with a controlled-release layer of ammoniomethacrylate polymer, EUDRAGIT® RS. Its efficacy to deliver an accelerated release profile *in vivo* was demonstrated using metoprolol succinate.

The objective of this study was to evaluate EUDRAMODE™ technology for a controlled-release system of terbutaline sulphate. The pharmacokinetics parameters achieved using this system were compared with the reference formulation (Bricanyl Duriles® controlled release formulation) in a crossover study in 18 healthy, adult human volunteers under fasting conditions. Deconvolution was performed from available pharmacokinetic data and an attempt was made to establish a relationship between the *in vitro* release data and *in vivo* plasma concentration profiles of the drug.

MATERIALS

Terbutaline sulphate (Hermes Chemicals) used was of USP grade. The following chemicals were obtained from commercial suppliers and were used as received: sodium citrate (Merck), Kollidon 30 (polyvinyl pyrrolidone, BASF Corporation), Aerosil-200 (colloidal silicon dioxide, Degussa AG), Imwitor 900 (glyceryl mono-stearate, SASOL), Tween 80 (polysorbate 80, Merck), talc (Luzenac), triethyl citrate (Morflex, Inc.), EUDRAGIT® NE 30D (polyacrylate dispersion 30% EP, Roehm GmbH & Co. KG), EUDRAGIT® RS

30D [ammonio methacrylate copolymer (EP-Type B), Roehm GmbH & Co. KG].

The reagents used for analytical purpose were of AR grade. The reference formulations of terbutaline sulphate were Bricanyl Duriles® (Astrazeneca GmbH) and Terbul tablets (Teofarma, S.r.l).

PREPARATION OF PELLETS

The pellets were prepared by multiple layering of a polymer coat (EUDRAGIT® NE) on a salt core (tri-sodium citrate) followed by drug layering and an outer polymer coat of EUDRAGIT® RS.

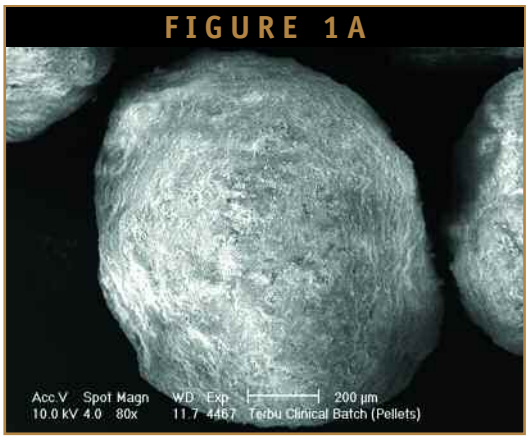
Commercially available salts were milled using a multimill at medium speed, knives forward (Clit Multimill, Model-CPMMMM), sifted (Vibratory sifter, Model-CPMVS-10) and the fractions between 600 to 800 microns were taken for the coating trials. These salt cores were coated with the neutral polymer layer (EUDRAGIT® NE) at a 5% w/w level. For EUDRAGIT® NE 30D coating, tween 80 at 2% w/w of polymer was used as a plasticizer, and glyceryl monostearate at 5% w/w of polymer was used as a glidant for optimum film formation.[13] The EUDRAGIT® NE coating was carried out in a fluid bed processor (Glatt GPCG 1.1,

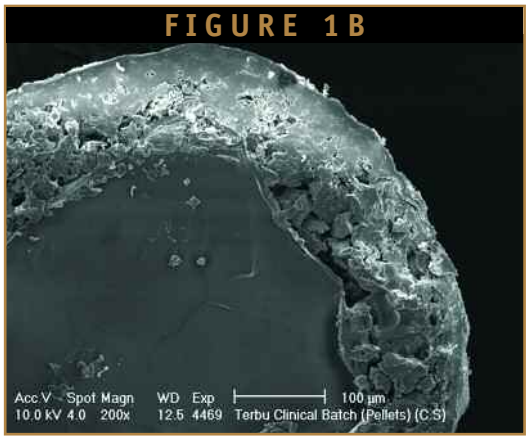
TABLE 1

Parameter	Criteria	Result
System Suitability	%CV ≤ 2%	Mean Area ratio ± SD 1.34 ± 0.0247 %CV= 1.84
Ruggedness (Effect of columns)	%CV ≤ 5%	Mean Area ratio ± SD 0.678 ± 0.0183 %CV= 2.71
Accuracy (Inter-batch)	85%-115%	LQC- 97.74% MQC- 91.06% HQC- 93.14%
Accuracy (Intra-batch)	85%-115%	LQC- 95.104% to 100.50% MQC- 87.87% to 92.58 % HQC- 89.77% to 94.92%
Precision (Inter-batch)	%CV ≤ 15	LQC- 8.83% MQC- 6.36% HQC- 8.50%
Precision (Intra-batch)	%CV ≤ 15	LQC- 6.32% to 12.97% MQC- 0.51% to 9.54% HQC- 4.62% to 11.37%
Freeze-thaw stability	≤ 85%-115%	LQC- 97.40% to 101.02% HQC- 98.38% to 102.61%
Injector stability at 10 hours	≤ 85%-115%	LQC- 103.70% HQC- 100.34%
Recovery	Mean = 86.92%	
Linearity range	0.50 ng/ml to 50 ng/ml	
Calibration curve	r^2 = 0.999	
Sensitivity	LLOQ- 0.53 ng/ml Accuracy at LLOQ- 106.68% (Criteria = 80%-120%) Precision at LLOQ- %CV=5.74% (Criteria = %CV ≤ 20%)	

Method validation parameters for plasma sample analysis.

MODULATED RELEASE





SEM of pellets (A) surface morphology (B) cross-section of the pellet showing salt core, modulating layer (EUDRAGIT® NE), terbutaline sulphate layer and controlled-release layer (EUDRAGIT® RS)

nozzle diameter 0.8 mm), using a bottom spray (wurster). The processing parameters were as follows: atomizing air pressure (1.5 to 2.0 bar); inlet air temperature (30ºC to 34ºC); spray rate (5 to 15 g/min); and product temperature (23ºC to 27ºC). Terbutaline sulphate was layered onto these EUDRAGIT® NE-coated salt cores. The binder solution (4% w/w Kollidon 30) was sprayed with simultaneous dusting of the drug (terbutaline sulphate) onto the cores to achieve a weight gain of 100% w/w. The drug layering was carried out in a conventional coating pan (Gansons CP-450GMP, nozzle diameter 1.0 mm) with the following processing parameters: rate of adding terbutaline dusting powder (10 to 15 g/min); pan speed (24 to 28 rpm); and binder spray rate (1.5 to 2.0 g/min). Drug content was analyzed to ensure uniformity of drug distribution (RSD ≤2 %) and these drug-layered pellets were further coated with EUDRAGIT® RS 30D using talc at 50% w/w of polymer and tri-ethyl citrate at 20% w/w of polymer as glidant and plasticizer, respectively. The EUDRAGIT® RS coating was carried out in a fluid bed processor as for the EUDRAGIT® NE coating with the similar processing parameters. The product temperature was maintained between 25ºC to 30ºC. After completion of the coating, the pellets were fluidized in the fluid bed coater at 40ºC for 1 hour and were further cured at 40ºC for 24 hours in a tray dryer. About 1% Aerosil 200 was added to the coated pellets while curing.

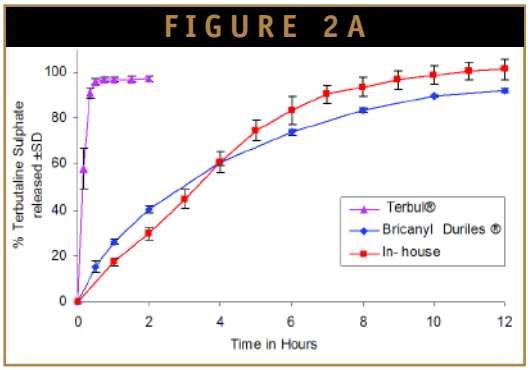
SCANNING ELECTRON MICROSCOPY

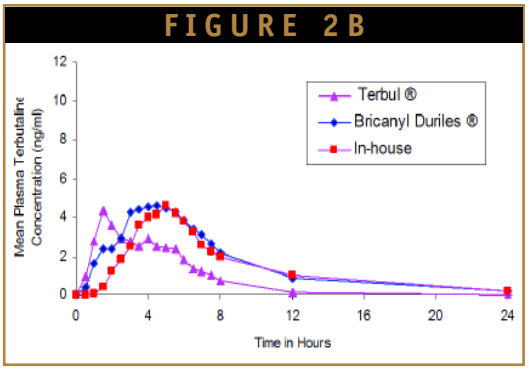
The pellets were examined for surface morphology and film thickness by scanning electron microscopy (SEM, Phillips XL30). Samples were gold-coated using a sputter coater and examined at 10 kv with tilted edges of 45 degrees. To evaluate the film thickness, pellets were radially sectioned before the sputter coating.

Figure 1 represents the scanning electron micrograph of the modulated-release pellets. The four layers [salt core, modulating layer (EUDRAGIT® NE), drug layer and the controlled-release layer (EUDRAGIT® RS)] could be clearly distinguished. At a 9% w/w level of the coating, a thickness of about 15 to 30 micrometers was obtained (n = 3, RSD < 6%).

IN VITRO DISSOLUTION STUDIES OF THE FORMULATION

In vitro dissolution studies were carried out in a USP type I apparatus (Electrolab-





(A) Comparative *in vitro* release profiles of the in-house controlled-release formulation with reference formulations (Bricanyl Duriles® & Terbul®). (B) Linear plot of mean plasma terbutaline sulphate concentrations versus time in 18 healthy human volunteers.

TABLE 2

	T_{max} (hours)			C_{max} (ng/ml)			AUC_{last} (ng.hr/ml)			AUC_{inf} (ng.hr/ml)			K_{el} (hr^{-1})		
	Formulation			Formulation			Formulation			Formulation			Formulation		
Mean	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C
SD	5.03	4.56	3.08	5.867	6.285	5.537	30.05	34.99	18.43	36.62	44.49	22.05	0.355	0.300	0.354
Min	1.120	1.340	1.740	3.456	5.531	4.311	25.97	38.74	15.99	33.23	47.92	18.27	0.327	0.181	0.147
Median	3.00	1.50	1.00	2.529	2.399	1.763	8.26	8.94	7.23	10.12	10.68	9.19	0.052	0.025	0.163
Max	5.00	4.75	2.75	5.107	4.413	4.742	21.72	22.94	13.76	26.32	29.69	16.79	0.207	0.294	0.322
CV%	6.50	7.00	6.00	18.478	26.914	19.692	123.45	179.88	74.259	158.07	219.11	87.54	1.150	0.664	0.740
Geometric Mean	22.23	29.38	56.52	58.910	88.010	77.880	86.44	110.72	86.78	90.66	107.72	82.84	92.27	60.40	41.75
	4.90	4.32	2.61	5.318	5.193	4.516	24.24	26.11	15.03	29.08	32.98	18.39	0.236	0.235	0.327

Pharmacokinetic data of the volunteers (n= 18). A= In-house, B = Bricanyl Duriles®, C = Terbul®

model TDT-8L) at 37ºC (n = 6), and the rotation speed was set at 100 rpm. The samples were quantitated chromatographically as per USP method against standard solutions of terbutaline sulphate using a Waters Alliance 2695 separation module with a Waters 2487 dual wavelength detector. The cumulative amount of drug dissolved was plotted verses time as percent dissolved drug. The release studies for the formulations were carried out in 900 ml of 0.1 N HCl (for 2 hrs) followed by phosphate buffer (pH – 6.8).

Figure 2A presents a comparative *in vitro* release profile of all three formulations. The reference controlled-release formulation (Bricanyl Duriles®) showed an initial 15% release in 0.5 hours followed by a continuous release with a zero-order profile with 80% release in 8 hours. The in-house controlled-release formulation showed initial 18% release in 1 hour followed by a continuous release with a zero-order profile with 90% release in 8 hours. The immediate-release formulation, Terbul, showed nearly 100% release in 1 hour.

The mechanism of drug release through the pellets prepared as per the system is diffusion controlled. During dissolution, the initial release of the drug from the pellets is through simple diffusion of the drug through the EUDRAGIT®RS layer. After the medium or water penetrates further into the pellets (across the inner neutral polymer layer) it dissolves the salt and results in the dissociation of the anions, which interact with the cations of the EUDRAGIT® RS film. Citrate ions inhibit hydration of EUDRAGIT® films, thus controlling the release of the drug and aids in achieving a desired release pattern.

IN VIVO STUDIES OF THE FORMULATION

The in-house controlled-release formulation of terbutaline sulphate (7.5 mg), reference controlled-release formulation (Bricanyl Duriles®, 7.5 mg) and reference immediate-release formulation (Terbul, 2 tablets X 2.5 mg) were selected for pharmacokinetic investigation in a randomized three-treatment, three-period, three-sequence, single-dose, crossover bio study (Courtesy: Vimta Labs Ltd.) in 18 + 3 (standby) healthy, adult, human subjects under fasting conditions. Pharmacokinetic parameters, such as C_{max}, $AUC_{0\rightarrow t}$, $AUC_{0\rightarrow\infty}$, T_{max}, K_{el}, and $t_{1/2}$, were determined. In each period, a total of 20 blood samples (5 ml each) were collected and analyzed for the plasma concentration.

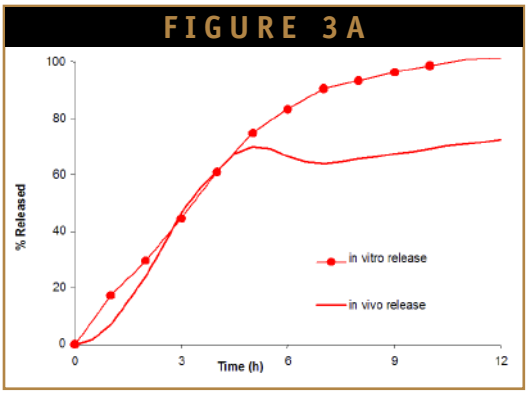
TABLE 3A - The FI for o.d. application

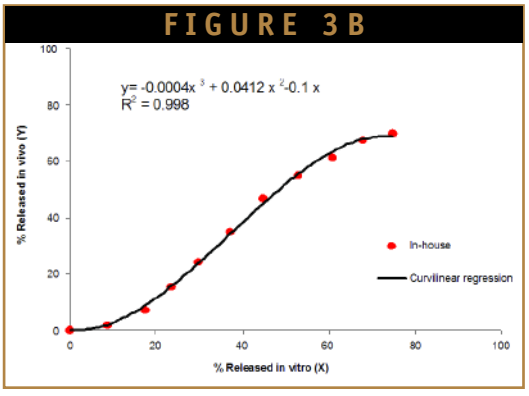
Product	Cs max	Css min	Css avg	Fluctuation Index
In-house	4.721	0.247	1.5	3.0
Reference (Bricanyl Duriles®)	4.786	0.216	1.7	2.8

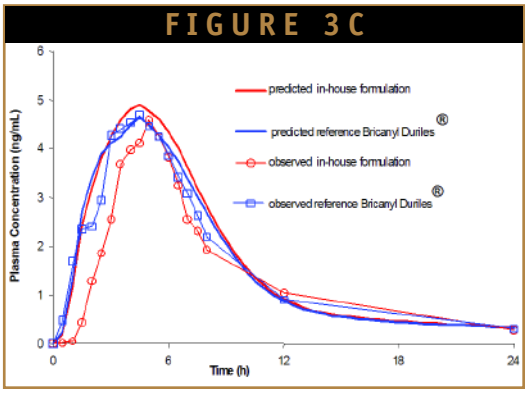
TABLE 3B - The FI for b.i.d application

Product	Cs max	Css min	Css avg	Fluctuation Index
In-house	5.343	1.255	29	1.4
Reference (Bricanyl Duriles®)	5.439	1.257	3.3	1.3

Fluctuation index (FI) for o.d and b.i.d application.







(A) Comparative *in vitro* and *in vivo* release profiles (calculated by deconvulation) of the in-house controlled-release formulation. (B) IVIVC model developed from *in vitro* and *in vivo* release data for the in-house formulation. (C) Predicted and observed mean plasma concentration profiles of terbutaline formulations.

DETERMINATION OF DRUG LEVELS FROM PLASMA

The concentration of terbutaline in human plasma was estimated using a precise, accurate and validated GC-MS procedure (Varian CP 3800). The mixture of the plasma samples and salbutamol (internal standard) were treated with sodium acetate buffer and loaded in solid phase extraction. The eluent was evaporated and reconstituted using pyridine followed by N, O-bis(trimethylsilyl) trifluro acetamide (BSFTA). This reconstituted sample was loaded onto the GC-MS system. The chromatographic and mass spectrometric conditions used were silica column (CPSIL 8CB); column temperature, 120ºC (hold 1 min) to 290ºC at the rate 30ºC (hold 5.37 min); injector, 1079 split injector; injector temperature, 270ºC; carrier gas, helium; flow rate, 0.8 ml/min and volume of injection, 2.0 microliters. The GC-MS procedure for the estimation of terbutaline sulphate in human plasma samples was validated for different parameters as listed in Table 1.

STATISTICAL ANALYSIS

Blood plasma concentration levels of terbutaline sulphate were considered for comparison of the in-house and the reference formulation. Maximal plasma concentration (C_{max}, ng/ml) and time to reach the peak concentration (T_{max}, hr) were obtained directly by the visual inspection of each subject's plasma concentration-time profile. The $AUC_{0\rightarrow t}$, $AUC_{0\rightarrow\infty}$, (ng.hr/ml), and $t_{1/2}$ (hr) were determined by non-compartmental analysis. The slope of the terminal log linear portion of the concentration-time profile was determined

FIGURE 4A

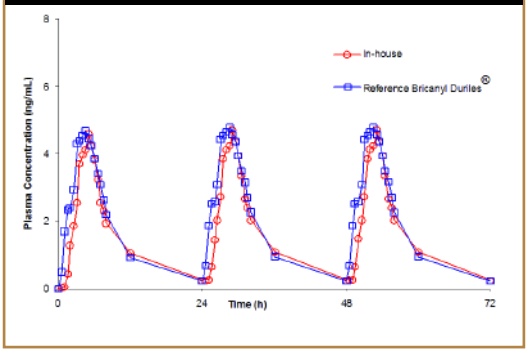
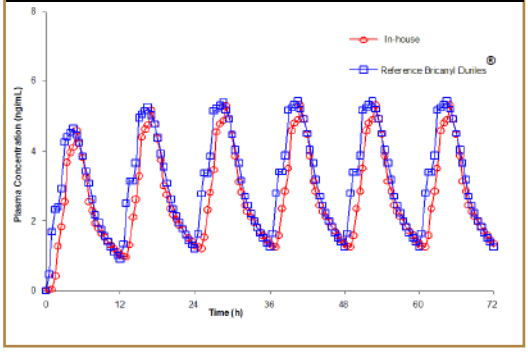


FIGURE 4B



Simulated plasma concentration profiles of terbutaline (calculated at steady-state) after application of the in-house formulation and the reference formulation. (A) Once daily application. (B) Twice daily application.

by least-squares regression analysis and used as an elimination rate constant (K_{el}, hr^{-1}). The elimination half-life was obtained from the formula, $t_{1/2} = \ln(2)/K_{el}$ (where ln is the natural logarithm). The $AUC_{0\rightarrow t}$ from time zero to the last quantifiable point (C_t) was calculated using trapezoidal rule and the extrapolated AUC from C_t to infinity ($AUC_{t\rightarrow\infty}$) was determined as C_t/K_{el}. The $AUC_{0\rightarrow\infty}$,was computed by the formula $AUC_{0\rightarrow\infty} = AUC_{0\rightarrow t} + AUC_{t\rightarrow\infty}$. All the pharmacokinetic parameters were calculated using LinMix procedures of WinNonlin Enterprise® Version 4.1 (Pharsight Corporation) software application. Statistical analysis was performed on logarithmically transformed data of C_{max}, $AUC_{0\rightarrow t}$, $AUC_{0\rightarrow\infty}$,using SAS System version 8.2 for Windows. (Courtesy: Vimta Labs Ltd.).

The in-house controlled-release formulation and the reference controlled-release formulation were similarly tolerated under single-dose, fasting conditions during the clinical phase of the study. The *in vivo* plasma concentrations versus time profile for the two formulations are represented in Figure 2B and the pharmacokinetic data from the comparative study is displayed in Table 2. Both the in-house controlled-release formulation and the reference controlled-release formulation showed similar pharmacokinetic parameters with T_{max} at about 5 hrs. The reference immediate-release formulation, Terbul, showed an immediate-release profile reaching T_{max} at about 2.75 hrs. Hence, it could be concluded that the in-house controlled-release formulation behaves similar to the reference controlled-release formulation *in vivo*.

IVIVC CORRELATION

The IVIVC was studied to identify a biorelevant *in vitro* dissolution medium for terbutaline sulphate. The *in vivo* release kinetics of terbutaline sulphate from the in-house and reference formulations were calculated from their plasma concentration levels using a numerical deconvolution method based on the trapezoidal formula.[14]

The calculations were performed with the following validated software: Microsoft Excel 2002 SP-2, Kinetica, Version 4.3 (InnaPhase Co.). Statistical Analysis System, SAS release 8.2 (SAS Institute, Inc.) courtesy of SAS/IML program language by Dr. F. Langenbucher/BioVista.

Figure 3A shows the plot of comparison of *in vitro* and *in vivo* release profiles of the in-house controlled-release formulation calculated by the numerical deconvolution method for time intervals up to 12 hrs. Figure 3B shows the plot of percentage released *in vivo* versus the percentage released *in vitro* for the same time points for both formulations. The *in vitro* and *in vivo* data were used for the development of the IVIVC model.

A quantitative relationship between the *in vitro* and *in vivo* release data was obtained using least-square regression. The resulting polynomial function describing the correlation of % released *in vitro* (X) and % released *in vivo* (Y) was as follows: $Y = 0.0004x^3 + 0.0412x^2 - 0.1x$, $R^2 = 0.998$. The value of R^2 demonstrated a significant correlation between the *in vitro* and *in vivo* time profiles.

Figure 3C shows the result for the internal predictability graphically and revealed that the predicted profiles were comparable to the observed profiles of the in-house and reference formulations.

SIMULATION OF STEADY-STATE PLASMA CONCENTRATIONS

The study of simulation of steady-state plasma concentrations of terbutaline after a multiple application of the in-house controlled-release formulation and the reference controlled-release formulation were calculated from single-dose data by

superimposition and addition of residual concentrations based on the elimination half-life (Figures 4A & 4B). The minimum and maximum observed plasma concentrations during a dosing interval at steady state ($C_{ss\ min}$ and $C_{ss\ max}$) for both the formulations were not significantly different. The fluctuation index for once and twice daily application was also calculated (Table 3). The differences seen in the fluctuation index from the in-house formulation and the reference formulation were not significant.

CONCLUSION

The *in vivo* release kinetics of terbutaline controlled-release formulation prepared using EUDRAMODE™ confirmed the *in vitro* release pattern and in comparison with a controlled-release reference formulation, provided similar availability of terbutaline sulphate in plasma. It could be concluded from this study that the *in vitro* dissolution behavior was reflected in the *in vivo* data for the formulation prepared as per this technology and significant IVIVC was obtained, which could be considered biorelevant. The study of simulation of steady-state plasma concentrations of terbutaline after a multiple application of the in-house controlled-release formulation and reference controlled-release formulation showed no significant difference. Thus, EUDRAMODE™ technology provides an effective alternative for the preparation of controlled-release systems and matching *in vivo* plasma profiles with existing formulations.

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BIOGRAPHIES

Dr. Hema Ravishankar serves as the Head of Degussa Pharma Polymers research centre in India. She heads a group of twelve scientists and her responsibility includes research and development in technologies for oral drug delivery. Her research focuses on pharmaceutical coatings, site specific delivery and optimization of pharmaceutical processes towards the need of the industry. She has more than 12 years experience in working in the pharmaceutical industry. During her tenure, she has successfully developed many advanced products in the field of oral drug delivery. Dr. Ravishankar earned her MPharm and PhD (Tech) from the University Department of Chemical Technology, Mumbai, India.

Dr. Jayanthi Iyer-Chavan is currently working as a Scientist in the Analytical Department at the Degussa Pharma Polymers research centre in India. Her most recent work was focused on development and optimization of analytical methodologies for EUDRAMODETM technology. She has a total experience of 4 years in the pharmaceutical industry in the analytical method development for solids, liquids, and semisolid dosage forms. She earned her MSc (Chemistry) from University of Mumbai and her PhD (Analytical Chemistry) from University Department of Chemical Technology, Mumbai, India.

Ms. Preeti Patil is currently working as a Scientist at the Degussa Pharma Polymers research centre in India. She has been involved in the research work for EUDRAMODE™ since 2002. Her research interests include optimization of release profiles for oral drug delivery systems, statistical analysis and different chromatographic analysis. She earned her MPharm in Pharmaceutical Analysis from University of Mumbai, India.

Ms. Ashwini Samel is currently working as a Scientist (Research Group Leader) at the Degussa Pharma Polymers research centre in India. Her most recent work was focused on development of EUDRAMODETM. She has a total experience of 8 years in the pharmaceutical industry in the development of oral dosage form that includes tablets, capsules, controlled-release dosage formss and site-specific oral drug delivery systems. She also has experience in scaling up of different types of formulations. She earned her MPharm in Quality Assurance from S.N.D.T. University, India.

Dr. Gerhard Renner is currently working for Degussa Pharma Polymers as Director Drug Delivery Technologies. He is responsible for the product line Drug Delivery Technology. Prior to his present engagement, he held various positions in R&D and Marketing & Sales, including Director R&D Europe and Global Product Manager at locations in Germany and in the US. Dr. Renner is author and co-author of various publications and presentations. He earned his PhD in Polymer Chemistry from the University of Bayreuth and conducted PhD research at the Pennsylvania State University, State College, PA.

Can Oral Controlled Drug Delivery Meet the Challenges Posed by Chronotherapeutics?

By: Neena Washington, PhD, and Professor Clive G. Wilson

INTRODUCTION

Traditionally, it has been taught that the homeostatic mechanisms of the body hold systems in equilibrium with little deviation, whilst allowing fluctuations to accommodate the body's changing demands and requirements. However, chronobiology has long recognized that biological systems alter with days or seasons, taking their cue from the environment (eg, mating seasons for animals and flowering seasons for plants), and that a "body clock" alters the overall homeostatic controls of the body. The magnitude to which a body clock affects almost all systems is still quite a new concept and has been shown to affect periodicity and/or amplitude. The best known of these is the circadian rhythm, which approximates to 1 day, and well-known examples are for growth hormone, which peaks during sleep, and levels of plasma testosterone and cortisol, which typically peak in the early morning. There are other rhythms, such as the ultradian, which are shorter than a day (eg, the milliseconds it takes for a neuron to fire or a 90-minute sleep cycle) and the infradian, referring to cycles longer than 24 hours (eg, monthly menstruation).

CHRONOTHERAPEUTICS: A NEW BRANCH OF THERAPY

What is less well-recognized is that the disease state of a body will also display a periodicity.[1] The realization that this occurs has led to the development of chronotherapeutics, a new branch of therapy. This aims to take maximum advantage of the disease's chronobiology to provide optimum plasma levels of drug, resulting in maximum health benefit and minimum side effects to the patient. This can be achieved by a combination of accurately timing both the dosing of the patient and the release of the drug from the delivery system. This new science is questioning the tradition of prescribing medication at evenly spaced time intervals throughout the day, in an attempt to maintain constant drug levels throughout a 24-hour period as more evidence is being obtained showing that improved efficacy can be achieved if drug administration is coordinated with day-night patterns and biological rhythms.[2]

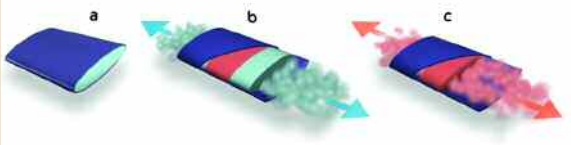
THERAPEUTIC BENEFITS & OBSTACLES

Chronotherapy has been shown to benefit patients in almost all disease areas (Table 1). For example, patients with both allergic rhinitis and rheumatoid arthritis often report that they suffer their worst symptoms when they wake up in the morning. Taking medication upon waking leads to a significant delay before symptoms are alleviated. Taking the medication the night before seems an obvious solution; however, medications, such as ibuprofen, need to be administered 4 to 6 hours before achieving their maximum benefit, so their peak effectiveness will occur prior to the patient waking, and the effect will be in decline as the patient wakes up.

Normal lung function undergoes circadian changes and reaches a low point in the early morning hours. This dip is particularly pronounced in asthmatics, and it has been estimated that symptoms of asthma occur 50 to 100 times more often at night than during the day. One method to treat the symptoms in the early hours is to use a long-acting bronchodilator; however, this produces sustained high doses of drug even when none is required, thus increasing the risk of unwanted side effects.

A better method of delivering drugs for diseases that display chronobiology is to use a time-delayed delivery method. The timing between administration of the formulation and release of the drug has to be carefully controlled. To perform this operation successfully and reproducibly, many factors have to be taken into consideration before the release characteristics of a dose form can be

FIGURE 1



Delayed release form of the Egalet®.
a) Intact unit, b) erosion of the time-delay inert plugs, c) drug release

specified for each disease state.

For oral drug delivery, it is important to understand not only how the gastrointestinal tract handles the dose form in both fasted and fed modes, but the effect of chronobiology motility. In the majority of cases, drugs must exit the stomach before they are absorbed. However, the residence time of an oral formulation is highly dependent on the presence or absence of food, and if food is present, the calorific value of the meal.

Gastric-emptying rates of the drug and its associated dose form present the most variable part of the whole gastrointestinal transit process.[4] Gastric emptying also demonstrates a circadian rhythm as identical meals empty significantly more slowly at 20 hours than at 8 hours, a factor that needs to be taken into account of dose forms taken upon retiring for drug release in the early hours of the morning.[5]

Enteric coating the dose form ensures that the time delay starts after exit of the dosage unit from the stomach, but the ultimate release from time of ingestion is now unpredictable. Once past the stomach, the small intestinal transit of dosage forms is relatively constant at around 4 hours.[6] However, the velocity of the migrating myoelectric complex (MMC), which controls the small intestinal transit of large, single units also displays a circadian rhythm as its speed of migration during the day is more than double that observed at night.[7] The advantage here is that units removed from the stomach by the MMC at night will have a longer time within the small intestine for drug absorption to occur.

TABLE 1

Respiratory	Allergic rhinitis, asthma
Inflammatory	Rheumatoid arthritis, related disorders
Neoplastic	Various forms of cancer
Cardiovascular	Hypertension, angina, myocardial infarction
Gastrointestinal	Peptic ulcer disease
Endocrinology	Hormonal deficiency

Selected diseases influenced by chronotherapy.[3]

MEETING THE CHALLENGES

It is obvious that chronotherapeutics represent a significant challenge to the drug delivery sector. The dosage forms have to cope not only with the significant physiological variations they will encounter, but they will have to precisely deliver their payload of drug to a specific time window. These parameters will vary from disease state to disease state as well as on the physiochemical and pharmacokinetic properties of each individual drug. One important factor for a dosage form to meet these challenges is that it needs to be very flexible and fully customizable.

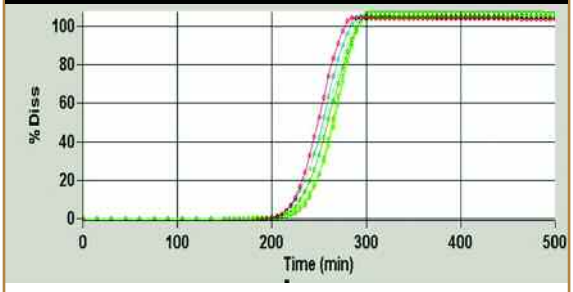
One of the newer oral drug delivery systems to the market is Egalet® (Egalet a/s, Denmark).[8,9] This technology is novel in that it uses erosion rather than diffusion as the method for drug delivery. Erosion of the matrix closely follows the penetration of water into the matrix, thus providing surface erosion control. Two forms of the Egalet technology exist, constant release and delayed burst release. The delayed burst release shows promise for chronotherapeutics.

The manufacturing process is conventional two or three color (component), injection molding. The premixed powders (usually in the form of extruded granulates) are used to form either the active matrix, plug, or coat; are fed into the mold; and feature a reciprocating injection-molding process that allows for sequential molding of the shell and the core contents within the dyes. This design provides an efficient manufacturing process coupled with high accuracy in dimensions, weight, and content.

The delayed-release form of the Egalet technology is illustrated in Figure 1. The system consists of an impermeable shell with two lag plugs, enclosing a plug of active drug in the middle of the unit. Time of release can then be modulated by the length and composition of the plugs. The shells are made of ethylcellulose and cetostearyl alcohol, while the matrix of the plugs comprises a mixture of polyethylene glycol monostearates and polyethylene oxides.

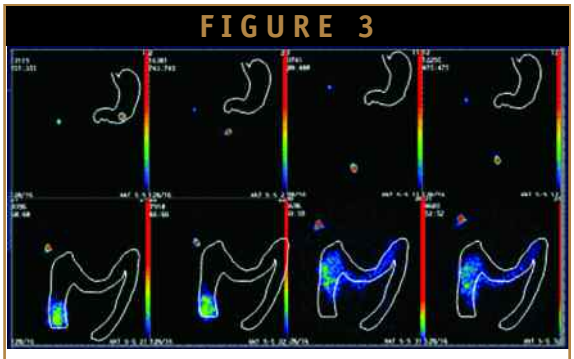
The matrix is designed to erode when in contact with available water, but at the same time, it is desirable that water does not diffuse into the matrix until the point of release, thus avoiding hydrolysis and diffusion and reducing the effects of luminal enzymatic

FIGURE 2



Graph demonstrating the *in vitro* reproducibility of hydrocortisone release from four delayed-release Egalet® units at 200 minutes.

FIGURE 3



Sequential images of the gastrointestinal transit and behavior of an Egalet® in a normal healthy volunteer (Time 0, 1, 2, 3, 4, 5, 6, 7 hours starting from top left hand corner).[11]

activity. The objective is to reach a balance in which the erosion is as fast as the diffusion of water into the matrix. To ensure a gradual release of the active substance(s), the matrix has to be eroded in a heterogeneous manner, the opposite of homogeneous erosion or erosion occurring simultaneously throughout the matrix.[10] The advantage of this is that the surface area that is exposed to water remains constant with time, resulting in zero-order performance (Figure 2).

The unit lends itself to several interesting possibilities for drug delivery, which may meet many of the exacting demands of chronotherapeutics, including:

- The diameter of the Egalet and the length of the inert plugs can be made to any length, thus tailoring the lag phase before drug is released from the core, so evening dosing to meet a requirement of drug release during the early hours of the morning is possible. The units can be enteric coated so that the delayed release "clock" starts ticking once the units have left the stomach.

- The Egalet can deliver two (or more) active substances at the same percentile rate per unit of time irrespective of the concentration of each drug, as long as the distribution of the active substances is uniform throughout the matrix.

- The same active substance can be used in the outer and inner plugs, but at a different concentration to create a customized-release profile.

Release of drug from the delayed-release Egalet formulation has been demonstrated in vivo using the gamma scintigraphy technique (Figure 3). This clearly slows the release of the radiolabelled core when the unit entered the ascending colon.[11] The released radioactivity gives a close approximation to the release and spread of the drug prior to absorption from the large bowel. The radiolabel can be seen to disperse as it passes through the ascending and transverse sections of the colon. Drug absorption usually ceases past the transverse colon due to the lack of water available.

SUMMARY

One of the key factors to successfully utilizing the Egalet technology for chronotherapeutics, prior to customizing the Egalet release characteristics, is to map the window of absorption, both in terms of time of absorption after oral ingestion and position within the gut at which the drug needs to be released. The chronobiology of the gut's motility needs to be understood and factored in. However, it does appear that this technology is adaptable enough to offer the field of chronotherapeutics a versatile and powerful tool. The FDA will give approval for chronotherapeutic labelling, thus opening up the potential for giving many well-established drugs a new lease of life.

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BIOGRAPHIES

Dr. Neena Washington has worked extensively both in academia and the pharmaceutical industry. She earned her BSc (Sp. Hons) in Physiology and Pharmacology from Sheffield University prior to earning her PhD in Pharmaceutics at Nottingham University. Her main areas of interest are the in vivo behavior of dosage forms and the use of imaging techniques, particularly gamma scintigraphy in the visualization of dosage form behavior in man. Her clinical interests are in the fields of gastrointestinal, respiratory, inflammation, and oncology.

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

PHOSPHOLIPIDS

General Trends in Liposome Preparations

By: Yoshio Nakano, PhD, and Hiroyuki Yamamura

INTRODUCTION

When phospholipids are added to aqueous solvent and given mechanical power at the phase-transition temperature or higher, they form closed capsules with an aqueous core. It has been more than 40 years since this lipid vesicle was named a liposome by Dr. Bangham in England. Now the liposome is one of the leading carriers of drug delivery systems (DDS) because it uses natural phospholipids or synthetic phospholipids and can contain either aqueous drugs or hydrophobic drugs. Compared with intensive use of liposome preparations for cosmetic products in Europe and other countries, only 7 liposome preparations are sold on the market as parenteral drugs (as of May 2005), and the number of drugs is only 4 (Amphotericin B, Doxorubicin, Daunorubicin, and Verteporfin). The number of launched drugs is small perhaps because there are pharmaceutical difficulties (eg, sterilization, mass production, homogeneity, assured reproducibility, and long-term stability), and the patent system is too complicated. The number of launched drugs, however, is expected to increase because the basic patent will expire before 2010. The following discussion will highlight some general trends in liposome preparations.

LONG-CIRCULATING POLYMER-MODIFIED LIPOSOMES

In the late 1980s, polyethylene glycol (PEG) began to be used for modifying the surface of drugs, such as proteins, to reduce antigenicity or ensure drug stability in blood. This technology was focused, and liposomes with surfaces modified by PEG derivatives were launched (Doxil/Caelyx, 1995).[1,2] The possible mechanisms for avoiding RES detection and prolonging retention in the circulation are: 1) a hydrophilic layer on the surface of the liposome to inhibit adsorption of opsonin molecules, complementing and inhibiting liposome uptake by the macrophage system; and 2) uptake of liposome is inhibited because of a nonspecific decrease in adhesiveness of liposome itself to macrophages. The molecular weight of PEG used for PEG-liposomes sold on the market is 2000, but stealth characteristics are effective when the molecular weight of PEG is between 1000 and 5000. PEG-conjugated phospholipids are used at approximately 6 mol% in all the lipids consisiting of the liposome, and the liposome diameter ranges from 100 to 200 nm.[3,4]

Furthermore, polyglycerin (PG), an oligomer of glycerin, can also show prolonged retention in the circulation when it is used as an aqueous high polymer instead of PEG.[5,6] Figure 1 and 2 show the basic structure of PEG-attached and PG-attached phospholipids that are available from NOF Corporation.

Other forms that have been shown to have the same effect include multi-arm PEGs, and aqueous high polymer lipid derivatives with phospholipids conjugated with alkenyl ether-maleic anhydride copolymerization.[7,8,9]

These stealth liposomes, with their diameter adjusted at about

FIGURE 1

PEG-attached phospholipid.

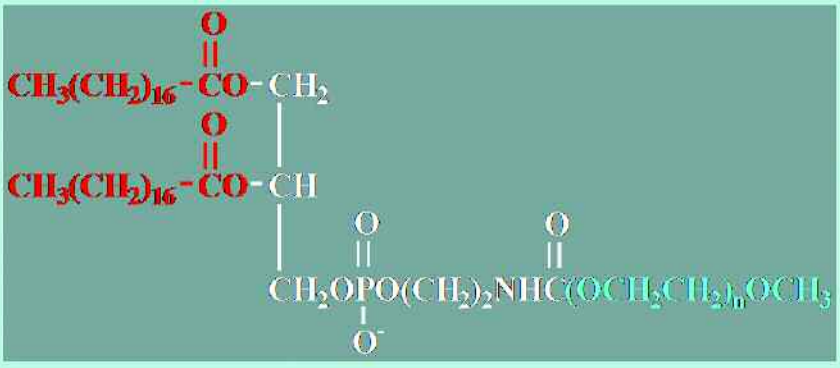
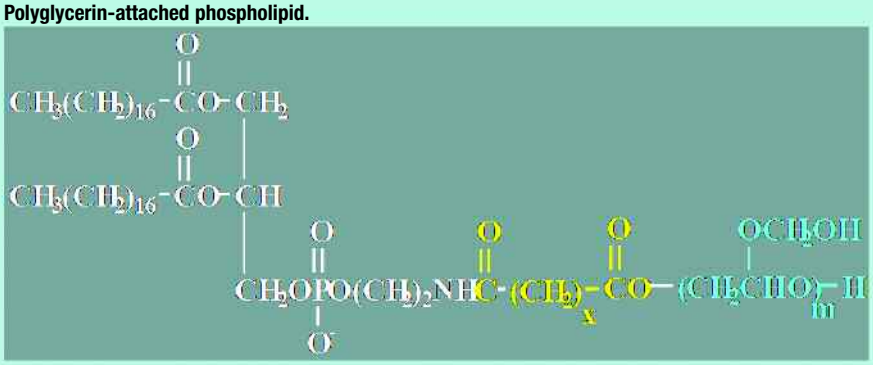


FIGURE 2

Polyglycerin-attached phospholipid.



100 nm, accumulate easily around tumor tissues because of the enhanced permeability retention (EPR) effect (proposed by Drs. Y. Matsumura and H. Maeda). Drug targeting to the tumor tissues is possible by incorporating anti-cancer drugs inside the liposome. The EPR effect means that polymerized drugs and liposomes are selectively trapped by tumor tissues and stay there for a longer period of time because of the following characteristics of tumor tissues: (1) high neovascular density; (2) wider intracellular spaces (100 to 200 nm) in insufficient vessel structure; and (3) vascular hyperpermeability.

As for commercial Doxil/Caelyx, Allen et al recently studied and reported the effect of liposome diameter[10]) and the kind of fatty acids.[10,11] According to their report, it was shown that a diameter below 157 nm is preferable, and a liposome with a 255-nm diameter has a slightly poorer tumor growth suppression. It is demonstrated that adjusting the diameter is the key to maximizing the EPR effect. Regarding fatty acids, the lower the phase-transition temperature replacing fatty acid in phosphatidylcholine (the main component) by oleic acid is, the less the tumor suppression effect. The drug delivery effect to the tumor site had been low because the stability of liposome in the circulation was impaired due to a lower phase-transition temperature.

IMMUNOLIPOSOMES

In an attempt to achieve active targeting using high-affinity binding of antibody to the target, immunoliposomes, liposomes with antibodies attached to their surface, was developed. Ordinary liposomes conjugated by antibody insufficiently avoids the reticuloendothelial system, so a PEG-modified liposome is necessary. Two types of approaches were considered; the antibody is conjugated directly to phospholipid, or to an end of the PEG chain. Experimental results indicated that binding to an end of the PEG chain is essential to preserve antigen recognition capacity.[12] Antibody-conjugated liposomes are also called pendant-type immunoliposomes because of their shape as shown in Figure 3. Pendant-type immunoliposomes are expected to play an important role in active targeting because they have long retention due to PEG and antigen recognition capacity thanks to antibody conjugation. But in the case of the IgG antibody, macrophages recognize it and uptake in the liver increases because macrophages have Fc receptors.[13] In order to solve this, an immunoliposome using Fab' fragment that lacks Fc region was prepared, and it was demonstrated by Maruyama et al to have longer retention after intravenous administration than IgG-PEG-liposomes.[14] The pattern of Fab'-PEG-liposomes disappearance in blood was the same as PEG-liposomes, and they had two stages of disappearance, namely an initial, fast disappearance due to phagocytosis by macrophages, etc and a

FIGURE 3

Aspects of an immunoliposome.

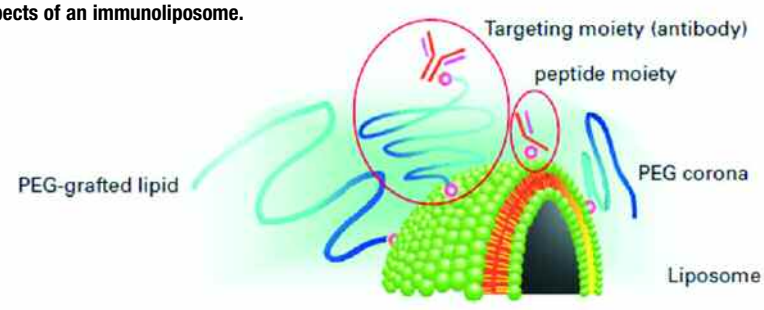
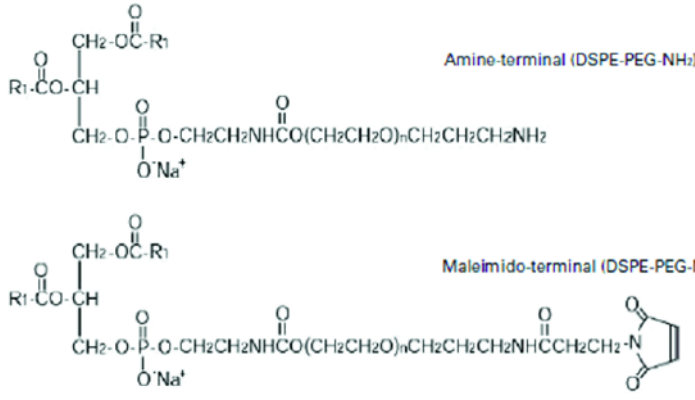


FIGURE 4

Activated PEG phospholipids for immunoliposomes.



late, slow disappearance.[15,16] Because longer retention was achieved using Fab'-PEG-liposomes, it was shown to avoid the initial uptake due to phagocytosis. From all these results, Fab' modification on the liposomal surface is considered to be effective in targeting using immunoliposomes. Figure 4 shows typical activated PEG phospholipids for immunoliposome formulations that are available from NOF Corporation.

TARGETING TUMORS

Recent progress in molecular biology and molecular embryology makes identification of various antigens appearing on tumor cells possible. Antigens that specifically appear on tumor cells include ganglioside GM3 on melanoma, MUC1, MUC2, and MUC3 on the surfaces of breast cancer, lung cancer, prostate cancer, and Lewis X on the surface of digestive cancer.[17-20] Antigens preferentially overexpressed on tumor cells are also reported, and those include transferrin receptor, folic acid receptor, CD19, and CD20.[21-24] Preparation of antibodies or ligands for these tumor-associated antigens, and binding them to the PEG end of PEG liposomes, may be effective for anti-cancer drugs to be delivered to tumor cells.

Nam et al made immunoliposomes using antibodies for Lewis X and ganglioside GM3 and studied the drug delivery.[23] Maruyama et al also reported the targeting effect using transferring-modified liposomes and anti-CD antibody modified liposomes.[25,26]

TRANSFERRIN (Tf) MODIFIED LIPOSOMES

Transferrin (Tf) is an iron-binding glycoprotein made up of single-chain peptides, and its molecular weight is 80,000. It is found in the blood in the concentration of 246 to 444 mg/dL, and involved in iron supply via Tf receptors on the surface of the cells. Together with increased angiogenesis, overexpression of Tf receptors is also observed in various tumor cells. The receptor is recycled after uptake of Tf into the cell, and there is no fusion with lysosomes after internalization. Therefore, Tf as the target ligand for tumor tissues may be very useful.

Iinuma et al studied liposomal uptake to tumor cells with time course using MKN45P, human stomach cancer cells. It was found that liposomes with Tf conjugated to an end of PEG-modified phospholipids is significantly easier to be taken in the cell than PEG liposomes without Tf.[25]

Iinuma et al further studied Cisplatin delivery to the tumor cells by preparing liposomes containing Cisplatin, injecting them into the abdomen of mice bearing MKN45P tumor cells, and studying the survival rate. It was also found that the more uptake by the tumor cells, the better the survival rate, and that Tf-modified liposomes are confirmed to be superior to normal liposomes and PEG-liposomes. Figure 5 shows the scope of Transferrin-attached liposomes and tumor uptake for active targeting.

TARGETING NEW BLOOD VESSELS

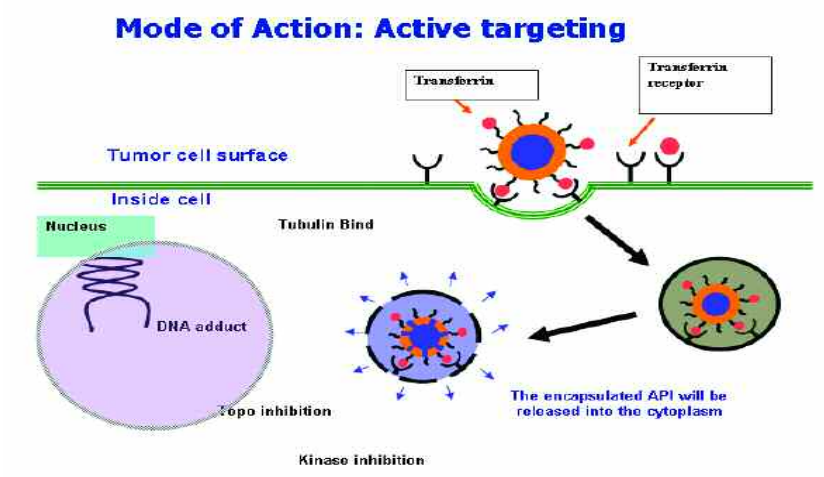
Targeting new blood vessels around tumor cells has also been tried.[27,28]

Oku et al screened peptides that have affinity with molecules that specifically appear on tumor-associated endothelial cells and conjugated the peptides to PEG-liposomes, thus trying to target tumor cells.[29]

Pastorino et al targeted aminopeptidase N, and conjugated NGR peptides to the PEG end of stealth liposomes that are made up of a PEG phospholipid (some amount of PEG phospholipid with reactive group should be added), and made stealth liposomes containing Doxorubicin. They also made stealth liposomes conjugated with peptides other than NGR, and more liposomes without any peptide binding to

FIGURE 5

Transferrin-attached liposome.



compare the target delivery.

In an animal experiment using mice, the uptake of NGR-peptide conjugated liposomes by neuroblastoma (NB) increased with time, and they were more than 10 times that of liposomes without any peptides at 24 hours. Almost no uptake occurred of liposomes modified by peptides with no targeting property.[30] NGR-peptides conjugate liposomes were only able to suppress the increase in tumor volume. This may be because it induced apoptosis in the endothelial cells of new vessels.

SUMMARY

We have discussed the general trends in liposome preparations, and in summary, the technology to achieve longer retention and better targeting is becoming the mainstream. We expect to see further utilization of these preparations in the clinical study and hope that new liposome preparations will be launched as soon as possible.

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BIOGRAPHIES

Dr. Yoshio Nakano is currently working as a General Manager in the phospholipids business, DDS Development of NOF CORPORATION. Dr. Nakano has worked for NOF CORPORATION since 1973 and spent 25 years as a researcher in lipid chemistry. He has more than 25 publications and patents while he worked in the Eastern Regional Research Center of the USDA as a visiting scientist between 1978 and 1981. He has established NOF's phospholipids R&D throughout the late 80s and early 90s. Dr. Nakano earned his PhD in Chemistry from Oita University Japan and his BS in Chemistry from Chiba University.

Mr. Hiroyuki Yamamura is the General Manager of the DDS Development Department in NOF CORPORATION. In 1970, he joined NOF CORPORATION; in 1984, he became General Manager of the Dusseldorf Office; in 1993, he became General Manager of the Marketing Department for Polymer Field; in 1995, he became General Manager of the Oleochemicals Research Laboratory; in 1998, he became General Manager of the Purchasing Department; and in 2001, he became General Manager of the DDS Development Department. He earned his BS in Chemical Engineering from Shizuoka University in 1970.

DRUG DELIVERY Executive

SUBCUTANEOUS PROTEIN DELIVERY – BREAKING THROUGH THE INTERSTITIAL MATRIX

Mark S. Wilson
Vice President, Business Development
Halozyme Therapeutics

"Pharmaceutical scientists should realize that they are no longer limited to subcutaneous injections of 1 to 2 mLs, and that high injection volume proteins don't necessitate IV formulation."

Founded in 1998, Halozyme Therapeutics is a biopharmaceutical company developing and commercializing recombinant human enzymes for the drug delivery, palliative care, oncology, and infertility markets. The company's portfolio of products is based on intellectual property covering the family of human enzymes known as hyaluronidases. The company has received FDA approval for two products: Cumulase®, the first and only recombinant human hyaluronidase for cumulus removal in the IVF process; and Hylenex®, for use as an adjuvant to increase the absorption and dispersion of other injected drugs. The versatility of the company's first enzyme, recombinant human PH20 hyaluronidase (abbreviated rHuPH20), enables Halozyme to develop the enzyme in product applications that include medical devices, drug delivery enhancement agents, and as therapeutic drugs. Drug Delivery Technology recently interviewed Mark S. Wilson, Vice President of Business Development, to discuss how the commercialization of the San Diego-based company's highly versatile enzyme technology within proven markets will enable the company to positively impact the quality of medicine.

Q: You had a strong turn-out for your presentation of Enhanze™ Technology at BIO 2006. Can you tell our readers a little about it?

A: Enhanze Technology is a revolutionary human enzyme-based drug delivery technology comprising co-formulations with our first approved enzyme-rHuPH20. This unique technology provides IV-like access from a subcutaneous injection.

In a randomized, well-controlled, double-blinded clinical study completed in the first quarter of this year, the use of this enzyme made it possible to deliver approximately 400 mL of lactated Ringer's solution in 1 hour subcutaneously. Some study subjects received up to 800 mL in 1 hour. This study used the enzyme to deliver a gravity-fed bag at a height of 100 cm and a 24-gauge needle without pumps. Pharmaceutical scientists know that one can deliver 1 to 2 mLs subcutaneously before pain and tissue distortion

dominate. rHuPH20 temporarily removes this barrier and opens up the possibility to inject quantities of therapeutics previously only possible by IV.

Q: What types of products are ideal candidates for the technology, and what is its effect on bioavailability?

A: The technology is focused on parenteral formulations but has utility for both large and small molecules.

In animal models, we have demonstrated an increase of systemic bioavailability approaching 100% following subcutaneous co-administration of biologics with rHuPH20. Many antibody therapeutics are about 60% bioavailable when delivered subcutaneously. Through the use of this Enhanze Technology, the increase in bioavailability can potentially lower the necessary dose, as 40% of the compound is not degraded locally. This can be very beneficial economically as well.

Q: Please describe the mechanism of action.

A: The rHuPH20 enzyme temporarily degrades hyaluronan (hyaluronic acid), a major component of the skin interstitium, and to a lesser extent, chondroitin-4 and -6 sulphate. This class of enzymes has been used for 50 years with an excellent safety profile. The new human recombinant product overcomes the limitations of the animal extracts, which were particularly impure and immunogenic due to contamination with bovine IgG as they were crude slaughterhouse preparations derived from bull testes.

Q: At what point should development scientists consider the use of this technology?

A: There are two key areas I believe are most relevant here. First, when a development program has completed Phase IIb, and shown that first indication of efficacy, and when the dose has been determined. Often it is at this point that pharmaceutical scientists confront the active ingredient's solubility and recognize that the dose cannot be delivered subcutaneously in a formulation of 1 to 2 mLs without frequent dosing. This is particularly apparent for monoclonal antibodies, which have a long half-life, but limited solubility. Using this technology, one can now avoid the need to give up the compliance and patient preference benefits of subcutaneous formulations for the traditional IV, which can generally only be administered in a hospital setting.

Secondly, the technology can bring new life to products that may be nearing the end of their patent lives or are "trapped" with IV delivery. With intellectual property covering these co-formulations until 2024, one can re-start and expand the lives of successful products. Of couse this can be a economic benefit, while also improving the product.

Q: What is the regulatory status of this enzyme, and what are the potential regulatory pathways by which a co-formulation could be approved?

A: rHuPH20 is approved in a medical device specific to the *In Vitro* Fertilization field in the US and EU, and in a biopharmaceutical product in the US (Hylenex, marketed by Baxter Healthcare).

The second part of your question is interesting. PH20 hyaluronidase enzymes have been approved with the indication "to enhance the absorption and dispersion of other injected drugs…" We believe that, depending on the therapeutic margin of the "other drug," the possible regulatory paths could be a supplemental filing supported by an abbreviated Phase IV pharmacokinetic clinical program, or a 505(b)(2) filing.

Q: This enzyme is also known as a "spreading factor." Can you explain?

A: rHuPH20 promotes the dispersion of other injected drugs in a dose-dependent fashion. In animal models, when the enzyme is injected subcutaneously with tracer dyes, the dispersion area is significantly increased. This can be extremely useful in reducing concentration-dependent injection site reactions (ISRs).

Q: What are the systemic effects of using this enzyme, and can you also discuss the safety profile?

A: The enzyme's half-life is less than 1 minute, so the effects are essentially local. The PH20 hyaluronidase class of enzymes has been used clinically for 50 years with an excellent safety profile. In another recent clinical trial of rHuPH20 evaluating the potential for allergic reactions, 0 out of 100 study subjects had an allergic response. It is also important to note that the body turns over more than 5 g of hyaluronan per day. The localized spreading effects disappear in about 24 hours due to reconstitution of the dermal barrier.

Q: Can you be more specific about some of the potential uses, perhaps for biologics?

A: With this technology, biopharmaceutical companies developing protein therapeutics are no longer limited by the 1- to 2-mL barrier. The ability to delivery a 10-mL push of an antibody in 1 minute could enable a subcutaneous formulation, with the concomitant benefits of improved patient compliance, favorable Part D reimbursement, and the possibility of home self-delivery. Most patients would rather receive treatments at home than in a hospital.

Another example would be an antibody that today, because of the perceived 1- to 2-mL subQ barrier, is now delivered once a week. Through this ability to deliver a larger dose subcutaneously and in combination with the long half-life of many antibodies, one can imagine developing a once-a-month subQ formulation. This could provide a substantial benefit to the patient while at the same time drive revenues and market share. Imagine what this could do for chronic injectables in the rheumatoid arthritis space.

Q: You have a successful partnership with Baxter. What are you doing to attract the attention of future potential partners?

A: Our pipeline is now at a stage that warrants complementary activities in addition to our traditional business development initiatives. When you are confident in your science, have valid data to back it up, and products on the market, it shows through our people and in our communication with our future potential partners. Publishing technology application articles as well as clinical trial results when appropriate is becoming imperative. We have embarked on a new business-to-business advertising campaign and are regularly presenting our developments at various major and local scientific conferences. In the near future, our efforts in these areas will become steadily more aggressive. ♦

Drug Delivery Showcase

Technology-Driven Solutions

Elan Drug Technologies (EDT) has unrivalled expertise in formulation, development, scale-up, and manufacturing to address drug optimization challenges of the pharmaceutical industry. The company offers a suite of proven and effective, technology-driven solutions. With more than 30 products launched in 40 countries, EDT has a proven track record of delivering success. The company's proprietary NanoCrystal® Technology offers superior results when coupled with poorly water-soluble compounds. The drug in nano-form can be incorporated into common dosage forms, with the potential for substantial improvements to drug performance. NanoCrystal technology has been applied in four products now launched in the US with more than $1 billion annually in market sales. EDT has a suite of more than 1,400 patents surrounding its technology-based solutions. For more information, contact Elan Drug Technologies at (610) 313-8867 or visit **www.elan.com/EDT.**

Controlled Release Technologies

Egalet a/s is a drug delivery company focusing on formulation and development of oral controlled-release products using its proprietary drug delivery Egalet® and Parvulet® technologies. The company has four products in clinical development, two of which are entering into late-stage pivotal studies. The Egalet tablet incorporates almost any pharmaceutical into a polymeric matrix eroded by body fluids at a constant rate. The tablet, made by a simple, unique injection-moulding technique, can be used for virtually any type of medicine and provides controlled release with precision and reliability. The Parvulet technology is a novel approach for pediatric drug delivery combining improved consumer acceptance with highly competitive development and production costs. Egalet aims to become a preferred partner for the pharmaceutical industry with its strategy for controlling drug development efforts from product formulation to clinical testing, regulatory submissions, and manufacturing. For more information visit Egalet a/s at **www.egalet.com.**

Advanced Delivery Technologies

Cardinal Health is the global leader in providing outsourced pharmaceutical development services, drug delivery technologies, contract manufacturing, packaging, and product commercialization services, serving the worldwide pharmaceutical and biotechnology industries. The company offers the broadest range of dose-form development and manufacturing options in the industry - from traditional and proprietary oral forms to sterile products, from inhaled forms to topicals. Cardinal Health holds more than 1,500 patents and patent applications for drug delivery systems. Technologies include soft gelatin capsules; Zydis® fast-dissolve dosage form; EnCirc®, EnVel®, and EnSolv® for oral modified-release products; lyophilization; inhaled technologies; and topical Microsponge® for timed-release and DelPouch® for unit dosing. For more information, contact Cardinal Health at (866) 720-3148 or e-mail pts@cardinal.com; or **visit www.cardinal.com/pts.**

New DDS Facility

NOF CORPORATION has been supplying Activated PEGs, high-purity phospholipids, and high-performance Polysorbate to pharmaceutical companies throughout the world. Its Activated PEGs have been used to conjugate with protein drugs so that PEG-stabilized drugs can circulate longer in the bloodstream with improved efficacy. NOF's new DDS plant for manufacturing Activated PEGs has started commercial operation under cGMP since October 2005. The new three-story, 200,000-sq-ft DDS plant now offers a five-fold increase in production capacity. The company's Activated PEGs and new plant have been attracting increasing attention from pharmaceutical companies across the globe. In addition, a new DDS Research Laboratory has just been established in the new building next to the DDS plant to accelerate the development of new products for DDS and satisfy customers. For more information, contact NOF Corporation at (914) 681-9790 or visit **www.nof.co.jp/dds.**

Drug Delivery Showcase

Iontophoresis Technologies

IOMED is a leader in the development, manufacture, and sale of active drug delivery systems that employ iontophoresis. IOMED's versatile transdermal and trans-scleral technology allows for custom delivery profiles for local and systemic applications. The company is actively pursuing opportunities to utilize its non-invasive drug delivery systems in combination with specialty pharmaceuticals to offer unique products designed to satisfy unmet medical needs. Licensing, co-development, and marketing agreements are available. For more information, contact IOMED at (801) 975-1191 or visit **www.iomed.com.**

Drug Development Services

DPT is the source for semi-solids and liquids — from concept to commercialization and beyond. Combining decades of expertise with unlimited production capabilities, DPT provides fully integrated development, manufacturing, and packaging solutions for biopharmaceutical and pharmaceutical products in semi-solid and liquid dosage forms. Drug development services range from preformulation, formulation and biopharmaceutical development, analytical development and validation, through process development. Specialized production capabilities include four cGMP facilities, clinical trial materials, full-scale commercial production, controlled substance registration Class II-IV, and complete supply chain management. Packaging services encompass engineering and procurement resources necessary for both conventional and specialized packaging. For more information, contact DPT at (866) CALL-DPT or visit **www.dptlabs.com.**

Controlled Delivery Platform

SCOLR Pharma applies its patented CDT® Controlled Delivery Technologies to develop formulations for companies with pharmaceutical, OTC, and nutraceutical products. These elegantly simple technologies can be used for controlled-release periods for up to 24 hours and can be manufactured using readily available standard materials and conventional production equipment. SCOLR Pharma partners with companies under contractual arrangements that include licensing fees, royalties, manufacturing contracts, or other mutually agreed upon financial arrangements. SCOLR Pharma's CDT® has the many distinct advantages, including highly programmable (capable of a wide range of release profiles), easy to manufacture (employs conventional manufacturing equipment), cost effective (utilizes standard tableting excipients), higher payload (when compared to other technologies), and strong patent protection (full patent life and easy enforcement). For more information, visit SCOLR Pharma at **www.scolr.com.**

Transdermal Development

3M adhesives are known for world-class performance across many applications. The synergy achieved through combination with other 3M core technologies will be put to work for it customers in designing transdermal solutions. 3M leverages more than 30 technology platforms to meet customer needs, and has a proven track record of success and global presence in transdermal delivery systems, including a 15-year history of development and manufacturing of Minitran™ (nitroglycerin) and Climara® (estradiol transdermal system), development of an estradiol/levonorgestrel combination patch, and numerous partner programs. 3M has transdermal products registered in more than 60 countries. For more information, contact 3M Drug Delivery Systems at (800) 643-8086 or visit **www.3M.com/DDS.**

Drug Delivery Showcase

Prefillable Delivery Systems

BD Medical - Pharmaceutical Systems is dedicated to developing prefillable drug delivery systems designed to fit the needs of the pharmaceutical industry. Whether a glass or plastic prefillable syringe, a nasal spray system, a dry drug reconstitution system, an injection or self-injection device, BD Medical - Pharmaceutical Systems provides the expertise and experience required by the pharmaceutical industry in a packaging partner. We deliver cost-effective alternatives to conventional drug delivery methods, which differentiate pharmaceutical products and contribute to the optimization of drug therapy. All of its prefillable devices are designed to meet healthcare professionals' demands for safety and convenience and to fulfill patients' needs for comfort. BD's worldwide presence, market awareness, and pharmaceutical packaging know-how allow it to propose suitable solutions for all regional markets and parenteral drug delivery needs. For more information, contact BD Medical - Pharmaceutical Systems at (201) 847-4017 or visit **www.bdpharma.com.**

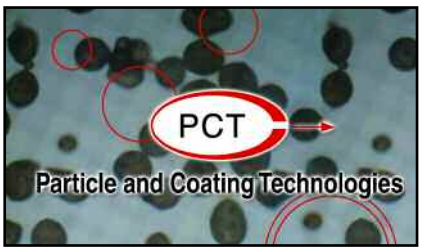
Contract Manufacturer/Supplier

Buender Glas GmbH is a business unit of the Gerresheimer Group headquartered in Duesseldorf, Germany. As a specialist in pharmaceutical glass systems, Buender Glas concentrates primarily on problem solutions relating to all aspects of injections. The company is an international technology leader in the growth market of prefillable syringes and cartridges. Its particular specialities include sterile all-glass syringe systems under the trademark RTF® (Ready-to-Fill). For the production of sterile syringes, Buender Glas has a unique technology center in which state-of-the-art ultrapure water-processing plants and clean-room systems in the 10,000 class set the basic standards. The company's products comply at least with the European, US, and Japanese pharmacopoeia requirements and are FDA registered. For more information, contact Buender Glas North America, Chris King, at (267) 895-1722 or visit **www.buenderglas.com.**

Formulation Solutions

SPI Pharma is a worldwide leader in custom formulation solutions for pharmaceutical and neutriceutical manufacturers. By offering raw materials, processing capabilities, and advanced application technologies, the company has become a valued source for complete custom delivery systems. This provides a competitive advantage for its customers' formulations. SPI's broad product line includes excipients, antacid actives, and formulated systems. All products are produced under cGMP manufacturing guidelines suitable for pharmaceutical and neutriceutical applications. Core processing capabilities include precipitation, hydrogenation, crystallization, spray drying, granulation, micronization, suspensions, and encapsulation. Some advanced applications include solid dosage formulation, viscous suspensions/blends, DC chewing gum, effervescent systems, chewable/quick-dissolve tablets, and customized granulations. For more information, contact SPI Pharma at (302) 576-8554 or visit **www.spipharma.com.**

Formulation Development



Particle and Coating Technologies, Inc., is a global leader in developing innovative pharmaceutical formulations and drug delivery techniques, including taste-masking formulations, bioavailability enhancement, and microprocessing - formulation development using gram to milligram amounts. PCT is a leader in utilizing advanced processing equipment technologies to spray dry and fluid bed coat unusually small amounts of active ingredient. These proven processes reduce development time and cost by allowing researchers to move into formulation development at an earlier stage. The company combines your active ingredients with its formulation and process development expertise to quickly turn concepts into marketplace realities. To find your unique solution, contact Dr. Irwin Jacobs of Particle and Coating Technologies, Inc., at (314) 535-1516 or **ijacobs@pctincusa.com.**

Drug Delivery Showcase

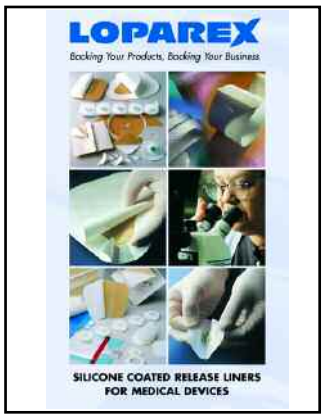
Self-Injection Systems

Ypsomed is the largest independent developer and manufacturer of custom-made self-injection systems. Pens range from simple disposable to those with variable dosing and electronic displays. Also manufactured are compatible pen needles with a unique click-on function for our own and other widely available pens. We are constantly expanding our core technology to cover new therapy and patient needs, including disposable and reusable auto-injector platforms for treating autoimmune diseases, cancer, and emergency therapies. A broad-based technology platform and over 150 patent families means Ypsomed can meet virtually all partner needs. All products are developed and manufactured in Switzerland, where capabilities include R&D, tool-making, moulding, clean-room production, and assembly facilities. Ypsomed manufactures in FDA-registered facilities and supplies devices approved for all leading markets. For more information, contact Ypsomed at +41 (0)34 424 32 23 or visit **www.ypsomed.com**

Advanced Spray Technology

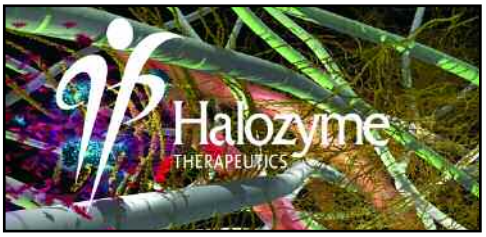
Spray Analysis and Research Services offers ways to improve and expedite drug delivery and manufacturing if you're looking for a new way to spray or have an existing coating, drying, or microencapsulation process that could benefit from optimization. A service of Spraying Systems Co., Spray Analysis uses advanced spray technology to help customers improve process efficiency and product quality, shorten development and testing time, and solve spray-related problems. Typical projects include tablet and device coating optimization, spray dry nozzle development and testing, atomizer prototyping, proof-of-concept tests, and spray characterization studies. For more information, contact Spray Analysis and Research Services at (800) 95 SPRAY or visit **www.sprayconsultants.com.**

Silicone-Coated Papers & Films



Loparex specializes in thin coatings on flexible webs in the manufacture of release liners for medical pressure sensitive adhesive (PSA) products. The major categories that define the medical PSA market include: Transdermal Drug Delivery Systems, EKG/ECG Electrodes and Electro-Medical Devices, and Wound Dressings. Key performance characteristics of release liners for medical PSA products include: complete traceability, cleanliness, moisture resistance, and die-cutability. Manufacturing release liners that satisfy the requirements of both manufacturer and end user is critical. Because of our continuing commitment to leading-edge technologies in chemistry and substrate development, Loparex is uniquely qualified to develop a release liner designed for your unique application. Look to Loparex for all your medical device release liner needs. For more information, contact Loparex, Inc., at (888) 327-5454, ext. 2671 or visit **www.loparex.com.**

Sub-Q Protein Delivery



Would you like to convert your drugs from IV to subcutaneous (Sub-Q) delivery or enhance the dispersion of your existing Sub-Q compounds? With Enhanze™ Technology, microgram quantities of a fully human recombinant enzyme act as a "molecular machete" to clear the subcutaneous "jungle." Based upon this mechanism of action, co-delivery with Enhanze is anticipated to permit the Sub-Q administration of large volumes (up to 10 cc) of antibody drugs, speed onset of action relative to Sub-Q delivery without Enhanze, and improve patient comfort. For more information, contact Mark Wilson, Vice President of Business Development (Halozyme Therapeutics) at mwilson@halozyme.com or (858) 794-8889; or visit **www.halozyme.com.**

DRUG DELIVERY Executive

AVEVA

AVEVA DDS, INC.: INNOVATIVE TRANSDERMAL TECHNOLOGY SOLUTIONS FOR PATIENTS, PARTNERS & PROFITS

Steven Sanders, PhD
Vice President, R&D
Aveva Drug Delivery Systems

"At Aveva, no single process is employed in the development of transdermal drug delivery systems. We create individualized systems for each pharmaceutical production process and partner, creating unique products to meet specialized needs, cost effectively and in less time than others within our area of expertise."

Aveva Drug Delivery Systems, located in Miramar, Florida, is a wholly owned subsidiary of the Nitto Denko company, one of the world's largest manufacturers of and a pioneer in transdermal drug delivery systems. Nitto Denko has a 20-year history of research and development of transdermal products. The medical division of Nitto Denko leverages the technologies available from other divisions of the company, such as proprietary, adhesive development and polymer synthesis to create innovative transdermal products. The US facilities have extended the core R&D and commercial production capabilities of Nitto Denko that have led to the success of numerous transdermal products in Japan. The opportunities for globalization of new transdermal technologies drive the current R&D environment within Aveva and Nitto Denko. Drug Delivery Technology recently interviewed Dr. Steven Sanders, Vice President of R&D at Aveva Drug Delivery Systems, to discuss how collaborations at his company's state-of-the-art transdermal research and manufacturing facility can strengthen product and development portfolios for its customers.

Q: What is Aveva's Mission Statement?

A: Aveva is committed to bringing innovative drug delivery solutions to the healthcare community through the commercialization of products with select industry partners. The fundamental aims of Aveva Drug Delivery Systems are much like the significant goals of Nitto Denko: develop products that are friendly to the environment and people; and help our industry partners by contributing to the prevention and prevention of disease and improving the quality of life for patients.

Q: How can transdermal products, especially those developed by Aveva, meet these goals?

A: Transdermal delivery is now a well-established and accepted route of administration for therapeutically beneficial medicines. The potential benefits that may be achieved using transdermal delivery include continuous, controlled release and absorption of medication into the body, avoiding presystemic metabolism that may occur following oral dosing, including both intestinal and hepatic first-pass metabolism, improving patient compliance by offering more convenient dosing regimens, such as once or twice weekly dosing, the ability to quickly discontinue treatment by removal of the system, etc. I could go on for some time about the benefits that may be realized with transdermal delivery, the key is to apply these benefits to a specific drug molecule and medical need in a manner that meets the goals. That is where the experience and expertise of the Medical Division Nitto Denko and Aveva comes into play: translating the technology into patient and environmentally friendly systems, which has been realized in our Gel Matrix adhesive, as well as improving the quality of life, such as with the only transdermal therapy for asthma, which is currently available in Japan. Our research and development scientists provide the backbone for product development. Our formulation development capabilities include proprietary computer-assisted transdermal feasibility evaluations, selection of excipients, adhesives, and structural film components based on function and compatibility, in conjunction with a high-capacity skin flux laboratory that provides the in vitro basis for preclinical evaluation of product prototypes. This is all conducted with active intellectual property assessment and development to protect and enhance product investments. An example of these efforts is the Crystal Reservoir Technology, which maximizes systemic drug absorption while conserving requirements for drug product incorporation into the actual patch.

Q: What cGMP development and production capabilities are in place in the Miramar facilities, and what is your record with the FDA and other regulatory authority inspections?

A: Our state-of-the-art facility was designed for multiproject development and product production with maximum flexibility. The facility has over 117,000 square feet of working space that accommodates: multiple blending suites (2.5 to 650 gal); 4 coating suites; 5 packaging suites; 4 commercial-scale packaging lines; 2 pilot-scale packaging lines; 43 separately controlled air-handling zones; and cooling units for special applications. Depending on client needs, our packaging lines are equipped for rotary punching, male-female punching, and island-cut punching, with scalable, batched production runs. The one-to-one ratio for manufacturing and packaging provides maximum efficiency during production. Our Miramar, Florida, facility maintains excellent working relationships with local, state, and federal regulatory offices, successfully hosting numerous inspections by the FDA and DEA. Currently, we hold three DEA licenses that cover: Research (Schedules 2-5); Analytical (Schedules 1-5); and Manufacturing (Schedules 2-5). Most importantly, we have an excellent compliance history. To date, we have not received any citations for DEA violations.

Q: Nitto Denko is Aveva's parent company, can you tell me a little about Nitto Denko's company history?

A: Nitto Denko, a global technology company with sales in excess of $5 billion, has facilities in 43 countries and employs more than 23,000 employees, 1,800 of whom are in the US.

Nitto Denko has extensive expertise in polymers and adhesives. This focus has enabled them to be a pioneer and one of the largest manufacturers of transdermal drug delivery (TDD) systems in the world, and number one in Japan with three of the most successfully commercialized transdermal patches. These products have contributed immensely to their partners' businesses. The work Nitto Denko has conducted on transdermal drug delivery systems has led to a number of awards, including: 1993 Technology Prize of the Adhesive Society of Japan; 1998 Science and Technology Agency Director's Prize; and 2001 PSJ Award for Drug Research and Development of the Pharmaceutical Society of Japan. The advancements in transdermal drug delivery systems haven't stopped there. Nitto Denko remains committed to leading the development of transdermal drug delivery technology and to continuing their contributions in the field of medical care to improve quality of life.

Q: You previously mentioned a couple of Aveva's leading-edge capabilities, can you provide some additional details on these transdermal technologies?

A: Two of the exciting technologies include our proprietary Gel Matrix adhesive and the Crystal-Reservoir drug-in-adhesive design. At the forefront of innovation, Aveva and Nitto Denko produced the first and only marketed transdermal patch using a revolutionary Gel Matrix adhesive system for an unequaled balance of adhesion reliability and gentleness. This acrylic polymer-based system combines the "skin-friendly" properties that are commonly associated with hydrophilic gels or plasters with the adhesion reliability of traditional acrylic matrix systems. Because the Gel Matrix adhesive cause only minimal effects to the stratum corneum, these patches can be removed and actually reapplied with minimal to no skin irritation. This leads to better tolerability of the transdermal product, improving patient experience and minimizing problems that patients may have with patch application and removal. Despite the gentle effects on the skin, the patches adhere consistently with minimal adhesion problems, lifting and actual patch fall-off occur rarely, also improving patient's satisfaction with treatment, which may lead to increased persistency and compliance. One of the most successful advancements in transdermal drug delivery systems is our Crystal Reservoir Technology, which has resulted in the ability to design smaller patches with better control of drug release. Techniques to oversaturate an adhesive polymer with medication leads to a partial and controlled crystallization of the drug in the adhesive matrix. The presence of drug molecules dissolved in the adhesive and in solid crystal form maximizes the thermodynamic activity that drives the absorption process. This provides a long-acting, consistent supply of drug in each patch as crystals redissolve. This technology also allows the potential use of lower amounts of drug in each patch with attendant economic and environmental benefits. Nitto Denko also brings innovative polymer synthesis capabilities that will aid in the development of future transdermal products. Critical for all polymer-based development projects is the ability to combine monomers into longer-chained polymers that retain the desirable characteristics of the initial building blocks. This technology has been applied to plastics and adhesives in a number of industries. Now, biopolymers are being utilized to incorporate DNA, siRNA, and proteins into biological systems, which are rapidly advancing the field of biotherapeutics and may find their way into transdermal systems of the future.

Q: Are there specific therapeutic areas of interest for transdermal products? What have been the limiting factors in developing more transdermal products?

A: There is no limitation on therapeutic area for the development of transdermal systems. Some therapeutic areas stand out, including sex hormones and pain management, due to the successful marriage of the individual drug molecules and available product technologies. To date, however, there are numerous transdermal products that have gained significant commercial success and provided unique benefits for patients. In addition to those mentioned previously, smoking cessation, hypertension, overactive bladder, and motion sickness are other areas with important transdermal products available. In some cases, the dominance of oral products in the US market has limited the entry of and better acceptance of transdermal products. The estrogen and combined estrogen/progestin treatments for menopausal symptoms represents one area where the benefits of transdermal therapy are not well understood. Continued research is necessary to fully appreciate the benefits of transdermal treatments, where transdermal delivery not only avoids effects on the liver that occur with oral dosing, but also provides treatment that matches the physiologically produced hormone. Certainly, challenges remain for the development of transdermal systems. Aveva is committed to finding new solutions that will minimize skin irritation or other effects that may be associated with transdermal delivery. By continuing our research, we can also break down the barriers that limit the types of drug molecules that may be delivered through the skin, with increased molecular size and complexity presenting current obstacles.

Q: What are some of Aveva's commercial successes, and what is in the pipeline?

A: In the commitment to improving the lives and well-being of patients, Aveva and Nitto Denko have driven numerous transdermal drug delivery systems successfully through the product development process. Aveva transdermal products are in various stages of development, ranging from initial research to regulatory review. We also have several proprietary developments with our partners that include both industry-leading pharma companies, as well as specialty pharmaceutical companies. The future looks very good for new transdermal products as technologies for improved designs continue to evolve. In addition, the current economic environment has placed an increased emphasis on discovering new value opportunities for currently marketed products as well as examining previous pipelines for potential missed opportunities in light of new drug delivery technologies. Aveva has demonstrated strength in the transdermal arena and will be seeking new alliances and opportunities to expand our available drug delivery platforms.

Q: Any closing comments for our readers about how they can work with Aveva to improve their pipelines or extend the life-cycle opportunities of their current products?

A: Bringing products to fruition efficiently and cost effectively deserves nothing less than a solid foundation of successful experience, coupled with a full range of research, development, and manufacturing capabilities, utilizing a number of sophisticated technologies. To accomplish this, our US and Japanese personnel work in a complementary, synergistic fashion. At Aveva, no single process is employed in the development of transdermal drug delivery systems. We create individualized systems for each pharmaceutical production process and partner, creating unique products to meet specialized needs, cost effectively and in less time than others within our area of expertise. Our strengths at Aveva and Nitto Denko are reflected in our successful collaborations with pharmaceutical and biotechnology partners. These include the following Transdermal Delivery Systems (TDDS): TEVA (Confidential); Pfizer (Confidential); Wyeth for the development of Lidocaine TDDS; Watson Laboratories, Inc., for the development of Nicotine Transdermal Systems; Par Pharmaceuticals, Inc., for the development of Clonidine TDDS; and Toa Eiyo for the development of Isosorbide Dinitrate TDDS. ♦

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When You Don't Like What You Hear

By: Dan Marino, MSc

Several years ago, I was working for a medical/pharmaceutical education company that created continuing education products in all forms, medical communication initiatives, as well as conducted medical advisory board programs for pharmaceutical companies. Originally, I was hired to manage all of the pharmaceutical and medical editorial content of the projects.

However, as it goes with working in a mid-size company, as you show your strengths and abilities, more responsibilities will be added to your job description, which is not always a good thing. One particular job function I was asked to perform included running a medical advisory board session for a very large pharmaceutical client. (I will not mention the name of the company or the drug for obvious legal concerns.) The session included medical and pharmaceutical directors from managed care companies, managers and directors from pharmaceutical benefit management (PBM) companies, and directors of employee health benefits from several large corporations.

Okay, enough with the boring part of this column. The idea, if you are not familiar with why the sessions are held, was to build advocacy among these thought leaders for our client's drug, which was a year or so away from pending approval. The company wanted to know if the managed care company or PBM would place it in a favorable position on its formulary and if the corporations would be willing to add it to their lists of approved medications for their employees.

Sounds simple, right? They watch numerous PowerPoint presentations explaining the disease and its symptoms, worker productivity costs, safety and efficacy studies of the drug, etc, and then tell me how wonderful it will be to have this drug available.

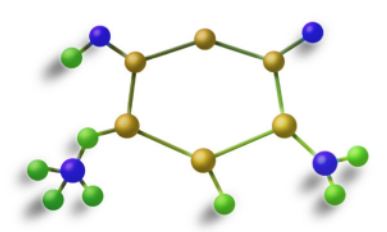
Well, it was the first time I attended one, let alone running one! So imagine my surprise when everyone in the room was moaning and complaining about how much it will cost, how the symptoms presented were too general to make an accurate diagnosis, how the disease was not life-threatening or life-altering, etc. As it was my job, I was feverishly writing down everything everyone was saying and thinking of all the praises I was going to receive from my boss in discovering how much money we could prevent our client from wasting should they pursue this drug any further. I couldn't wait to submit my report.

At that stage in my career, my areas of expertise were limited to the science behind the medicine, I was absolutely clueless regarding the business and economics of the pharmaceutical industry. So when I was called into my boss' office after I submitted my field report, rather than receiving a raise and a promotion, I was being scolded for what he called "doing it all wrong!"

The reality was, as everyone in this industry knows, is that there is an obscene amount of money and time spent on the development of a drug, and I was told that no pharmaceutical company at this stage of development wanted to pay $25,000 for a session that resulted in negative feedback. My report was simply something the company did not want to hear, especially at that point.

It was a just about a year later when the drug hit the market. The name was different, but after doing some recent research, it turned out that sales were and are much less than expected, it ended up with an unfavorable position on the formulary, and for a disease that supposedly is very common, I never met anyone who had it to this day. However, for years I saw DTC advertising in the form of television commercials. Who knows how much was spent in other forms of post-launch marketing activities.

The point of this column is to convey to my loyal readers that I do not believe in the saying "We have come too far to go back." Sometimes you will hear what you do not want to hear in your professional as well as personal life. In my opinion (and I am by no means telling CEOs of any companies that I know more than they do) it is best to listen more carefully to the negatives and sometimes make the hard and costly decision to terminate a development program (no matter the stage). The alternative can be much more expensive! ♦



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