Drug Delivery® Technology

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Breakthrough Cancer Pain Challenges

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

Ms. Cindy H. Dubin
Analytical Laboratories: Trends, Management & Relationships

Taneli Jouhikainen, MD, PhD, MBA
Addressing the Analgesic Gap in Breakthrough Cancer Pain

Mr. Daniel Ruppar
Hurdles in Oral Product Development & the Need for Continued Investment

IN THIS ISSUE

INTERVIEW WITH SCOLR PHARMA'S PRESIDENT & CEO

MR. DANIEL O. WILDS

FEATURING

SPECIALTY PHARMA Strategies For Business Development

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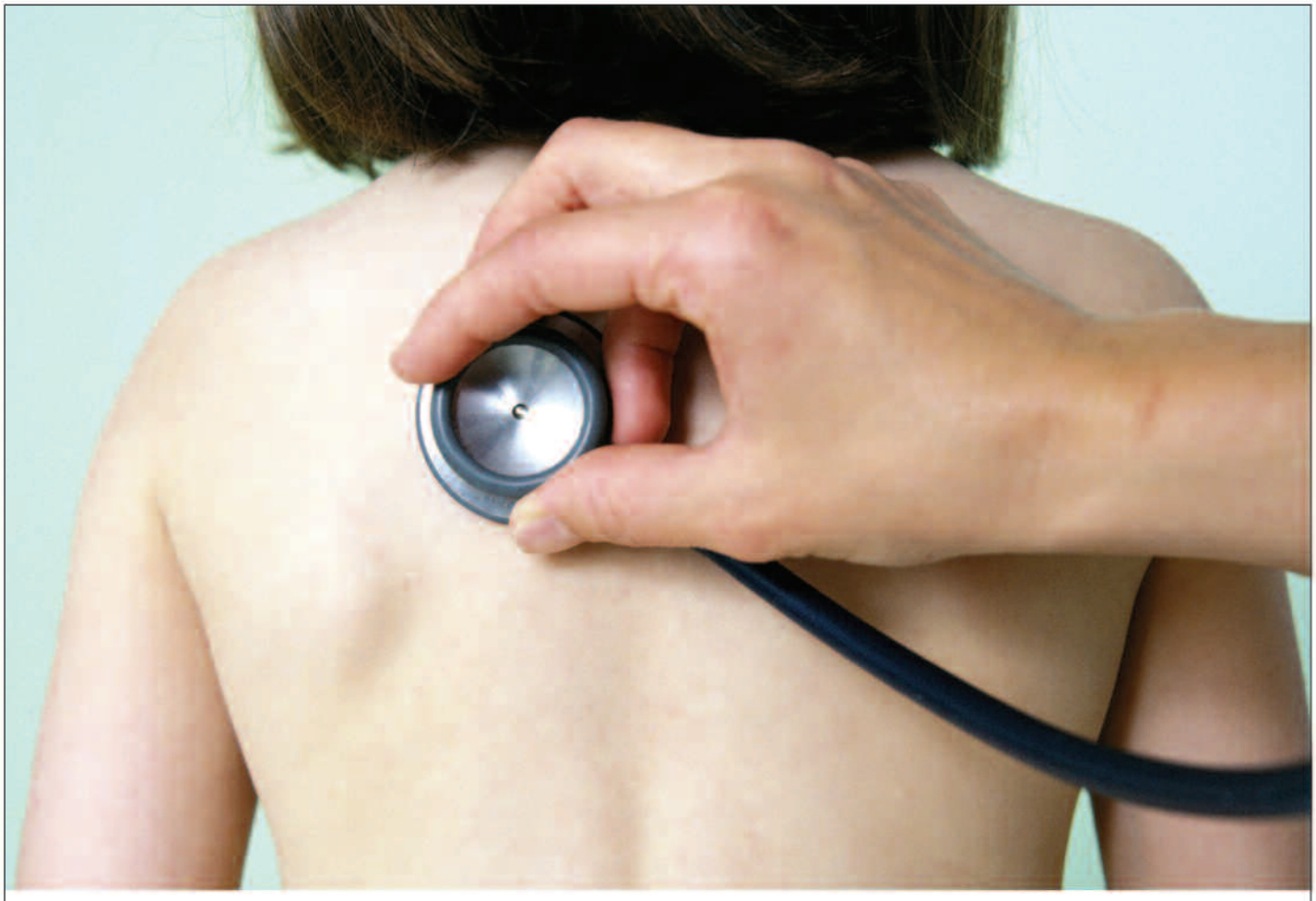

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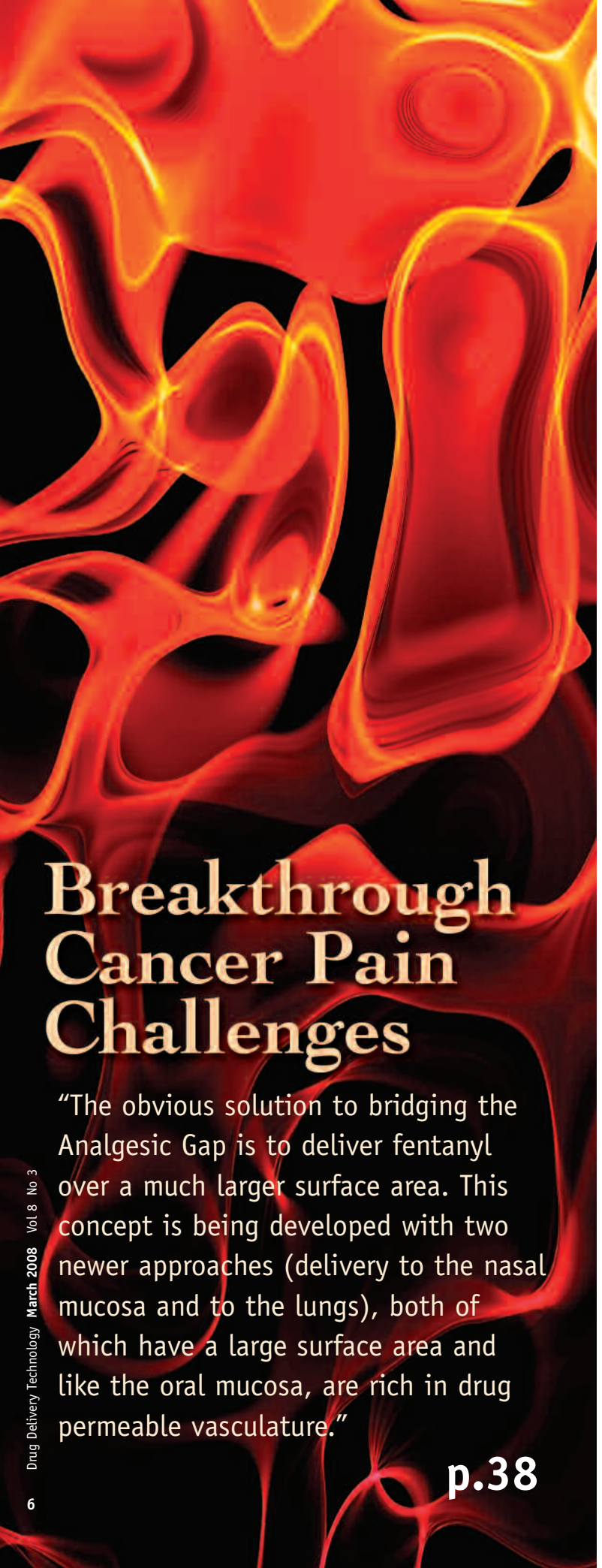
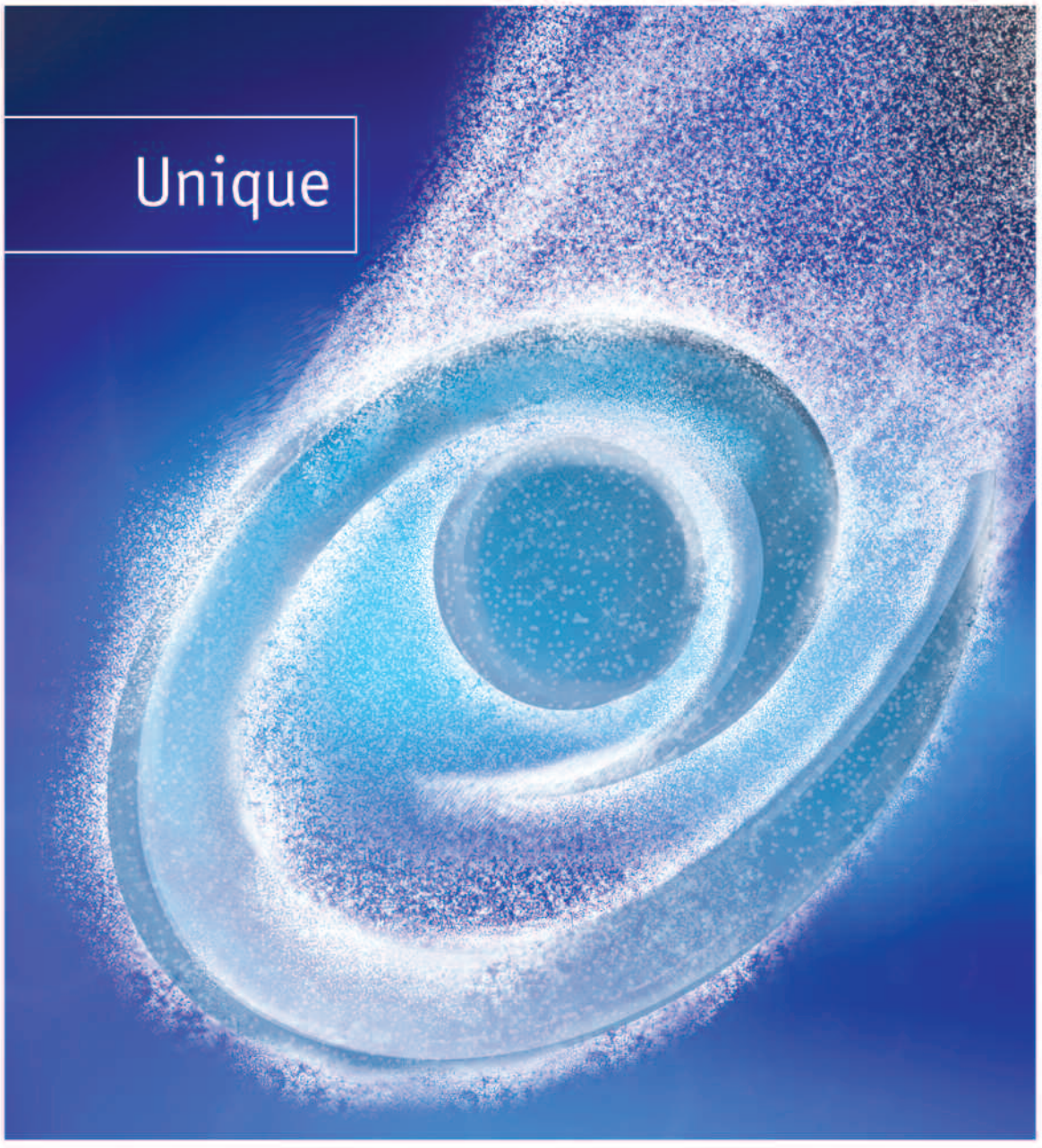


Breakthrough Cancer Pain Challenges

"The obvious solution to bridging the Analgesic Gap is to deliver fentanyl over a much larger surface area. This concept is being developed with two newer approaches (delivery to the nasal mucosa and to the lungs), both of which have a large surface area and like the oral mucosa, are rich in drug permeable vasculature."

p.38

Table Of Contents



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Analytical Lab Trends

"Pertinent questions the client should ask the laboratory are: 1) Does the laboratory have detailed and current SOPs and an effective quality group; 2) Has the laboratory been successfully audited by the FDA recently; 3) Does the laboratory have the instrumentation and the level of expertise needed for the project; and 4) Is it possible to discuss data directly with the analysts working on your project?"

p.66

Table Of Contents

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Market News and Trends

Ophthotech Begins Phase I Trial for Treating AMD

Ophthotech Corp., a privately held biopharmaceutical company focused on developing ophthalmic therapies for back-of-the-eye diseases, recently announced that the first patient has been enrolled in its Phase I clinical trial for the treatment of wet age-related macular degeneration (AMD). The Phase I trial will assess the safety and tolerability of E10030, an anti-PDGF aptamer, in combination with an anti-VEGF agent. This trial will enroll up to a maximum of 36 patients.

"The current treatment regimen for angiogenesis in AMD does not result in neovascular regression. The combination of anti-PDGF and anti-VEGF agents has been shown to cause neovascular regression, in both ocular and tumor angiogenesis preclinical models. We believe E10030 holds great promise for enhancing the visual outcome for patients with AMD," said Samir Patel, MD, President and CEO of Ophthotech Corp.

E10030 is the first of three compounds that Ophthotech is developing to treat AMD. Additional molecular entities include ARC1905, a complement (anti-C5) inhibitor, and volociximab, an anti-angiogenesis monoclonal antibody targeting alpha-5-beta-1 integrin.

E10030 is an aptamer-based compound directed against PDGF-B. Pharmacology studies indicate that E10030 binds to PDGF-B with high specificity and affinity and inhibits the functions of PDGF-B both in vitro and in vivo. In preclinical studies, E10030 demonstrated the potential to regress neovascularization when used in combination with a VEGF-A inhibitor. In experiments involving models of ocular vascularization, concurrent inhibition of PDGF-B and VEGF-A signaling was superior to inhibition of the VEGF-A pathway alone.

Anti-C5 aptamer ARC1905 inhibits C5, a central component of the complement cascade, which plays multiple roles in innate immunity and inflammatory diseases. Inhibition of this key step in the complement cascade at the level of C5 prevents the formation of key terminal fragments (C5a and C5b-9) regardless of which pathway (alternate, classical, or lectin) induced their generation. The C5a fragment is an important inflammatory activator inducing vascular permeability, recruitment, and activation of phagocytes. C5b-9 is involved in the formation of membrane attack complex (MAC: C5b-9), which initiates cells lysis. By inhibiting these C5-mediated inflammatory and MAC activities, therapeutic benefit may be achieved in both dry and wet AMD.

Volociximab is a monoclonal antibody targeting alpha-5-beta-1 integrin, a key protein involved in the formation of new blood vessels, a process known as angiogenesis. Alpha-5-beta-1 integrin is a critical survival factor for proliferating endothelial cells involved in angiogenesis. Inhibition of alpha-5-beta-1 integrin has demonstrated potent anti-angiogenic effects in multiple pre-clinical models of angiogenesis.

AMD is the leading cause of blindness for people over the age of 50 in the US and Europe. The wet form is characterized by the growth of new blood vessels into the central region of the retina. These new vessels cause severe visual loss due to retinal damage caused by subsequent leakage and scar formation. Anti-VEGF therapies and photodynamic therapies have been approved for wet AMD. Dry AMD accounts for up to 90% of all cases of AMD. There is no approved therapy for dry AMD, which afflicts 8 million patients in the US and an additional 8 million in Europe. Visual loss in dry AMD is typically not as severe as wet AMD; however, over time, dry AMD can progress to the wet form of the disease.

Ophthotech plans to develop a pipeline of compounds with strong scientific foundations for the treatment of AMD and bring them to market in an accelerated manner. In August 2007, Ophthotech announced a $36-million Series A venture financing and two separate in-licensing deals with Archemix Corp and (OSI) Eyetech, Inc. A third in-license from Biogen Idec and PDL BioPharma was announced in January 2008.

Dr. Reddy's Announces Collaboration With SkyePharma for New Product Utilizing Two of SkyePharma's Proprietary Drug Delivery Systems

Dr. Reddy's Laboratories recently announced that it has entered into an agreement with SkyePharma PLC to undertake a feasibility study of a product utilizing two of SkyePharma's proprietary drug delivery systems. The costs of this study will be paid by Dr. Reddy's. SkyePharma will also receive an up-front payment. If the feasibility study is successful, full development activities will begin later this year.

"We are very pleased to enter into this collaboration with Dr Reddy's on a new product development opportunity and hope to extend the collaboration to other products," said SkyePharma's Chief Executive Officer, Mr. Frank Condella.

Dr. Reddy's Laboratories was established in 1984 in Hyderabad, India, and is a global pharmaceutical company with proven research capabilities. Dr. Reddy's conducts research in the areas of diabetes, cardiovascular, anti-infectives, inflammation, and cancer. The Indian-based company produces finished dosage forms, active pharmaceutical ingredients, and biotechnology products that are marketed globally, with focus on India, US, Europe, and Russia.

Using its proprietary drug delivery technologies, SkyePharma develops new formulations of known molecules to provide a clinical advantage and life-cycle extension. The company has 12 approved products in the areas of oral, inhalation, and topical delivery. The group's products are marketed throughout the world by leading pharmaceutical companies.

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Market News and Trends

Abbott Laboratories Receives FDA Approval for Novel Combination Medicine for Comprehensive Cholesterol Management

Abbott Laboratories recently received US FDA approval for Simcor, the first fixed-dose combination of two widely prescribed cholesterol therapies, Niaspan (Abbott's proprietary niacin extended-release) and simvastatin. Simcor is approved for use along with diet to lower levels of elevated total cholesterol, LDL (bad) cholesterol, and triglycerides and to raise HDL (good) cholesterol in patients with complex lipid disease when treatment with simvastatin or Niaspan monotherapies are not considered adequate.

"Managing cholesterol encompasses many factors, not just lowering LDL," explained Christie Ballantyne, MD, the Methodist DeBakey Heart and Vascular Center, Houston, and lead Simcor investigator. "There is a clear need for medicines that both raise good and comprehensively lower the bad components of cholesterol. Simcor represents an important new option to help patients reach healthy lipid levels."

An estimated 80 million Americans have high levels of the bad LDL cholesterol, and more than 44 million have low levels of the good HDL cholesterol, which the body uses to remove bad cholesterol from the bloodstream. Studies have shown that along with diet, Simcor can help patients with lipid disorders reach their treatment goals by addressing more than just bad cholesterol, targeting multiple lipids with one pill.

The FDA's approval was based on Simcor safety and efficacy trial data from more than 640 patients with mixed dyslipidemia and type II hyperlipidemia. In the SEACOAST clinical trial, patients receiving Simcor 1000/20 mg achieved significant cholesterol improvements over and above what simvastatin 20 mg alone provided. Patients treated with Simcor 1000/20 mg had additional lipid improvements beyond simvastatin 20-mg treated baseline, with additional LDL reductions of 12% and an additional 21% HDL increase compared to a 7% decrease in LDL and an 8% increase in HDL with simvastatin 20 mg alone. Furthermore, Simcor reduced triglycerides by an additional 27% compared to 15% with simvastatin 20 mg alone.

Simcor was generally well tolerated by patients in clinical studies. Six percent of patients discontinued therapy due to flushing, the most commonly reported side effect of Simcor and niacin-based therapies. Flushing can be minimized by taking aspirin or an NSAID 30 minutes prior to taking the medication at bedtime. Flushing may subside over several weeks of consistent Simcor use.

"With Simcor, doctors now have a new option for helping patients reach their LDL and HDL cholesterol treatment goals with a combination of two proven therapies," said Eugene Sun, MD, Vice President of Global Clinical Development for Abbott. "Abbott is committed to bringing forward new cholesterol therapies, and Simcor represents a new treatment option for patients in Abbott's rapidly expanding portfolio of cholesterol treatments for lipid disorders."

The American Heart Association, National Cholesterol Education Program (NCEP) and American College of Cardiology recommend more aggressive treatment of HDL to reduce cardiovascular risk. Cholesterol and other lipids can build up in the bloodstream forming plaque and restricting blood flow, which can lead to heart disease. According to NCEP guidelines, a reduction in LDL of 1% is associated with a 1% reduction in heart disease risk. Additionally, raising HDL by 1 point is associated with a 2% heart disease risk reduction.

Abbott is committed to the continued research of its products and has sponsored the National Heart Lung and Blood Institute's AIM-HIGH outcomes study. The study is designed to evaluate the effects of niacin extended release and simvastatin in reducing cardiovascular events in patients with existing heart disease. AIM-HIGH began enrolling patients in 2005 with final results expected to be reported in 2011.

Abbott is a global, broad-based healthcare company devoted to the discovery, development, manufacture, and marketing of pharmaceuticals and medical products, including nutritionals, devices, and diagnostics. The company employs 65,000 people and markets its products in more than 130 countries.

New State-of-the-Art Packaging Rooms Increase Capacity & Flexibility for Bilcare Global Clinical Supplies

Bilcare Global Clinical Supplies, the single-source provider for global clinical supplies and services, recently announced the completion of an important phase in its capital improvement program that substantially increased and upgraded the capacity and flexibility of its primary and secondary packaging rooms. The company has added 6 new state-of-the-art packaging rooms and upgraded 20 others. Bilcare GCS now has 10 primary and 16 secondary packaging rooms at its 153,000-sq-ft US operation.

"The expansion and upgrading of our facilities and equipment is part of an ongoing and comprehensive effort to provide world-class service to our customers," said Bilcare Global Clinical Supplies, Americas, President Vincent Santa Maria. "Now more than ever, Bilcare GCS has the capacity, expertise, and capability to manage any project and to provide quality and service beyond compliance."

During the second half of 2007, Bilcare GCS expanded its storage and distribution facility (72,000 sq ft), installed PRISYM Medica labeling system software, increased its stability storage capacity and its formulation and analytical service capacity, and enhanced its IVRS/IWRS capabilities.

"These capital improvements combined with our experienced staff of project managers and our large global footprint in Europe and Asia sends a clear message to the industry that Bilcare GCS is the place for your clinical supply projects," said Mr. Maria.

Bilcare GCS serves the Americas, Europe, and Asia with clinical trial materials support, services, and complete project management. Its services for solid, semi-solid, liquid, DEA (CI-V), and biotech clinical trial materials (CTM) satisfy a broad range of requirements from preformulation research and development, analytical services, and clinical supplies packaging and labeling to IVRS, controlled temperature (cold and frozen chain) CTM storage, distribution worldwide, and returns and destructions accountability.

Antisense Therapeutics Licenses ATL1102 to Teva Pharmaceutical Industries

Antisense Therapeutics (ANP) Ltd. recently announced that the company had entered into an exclusive, worldwide license agreement with Teva Pharmaceutical Industries Ltd. to develop and commercialize ATL1102, a drug discovered by Isis Pharmaceuticals Inc. and licensed to ANP.

Under the terms of the agreement, ANP will receive an initial $2-million up-front payment and has the potential to receive payments related to the continued clinical development of ATL1102 for MS upon certain future development milestones, with more significant milestone payments for entry into the market, and sales targets in particular territories. The license includes potential milestone payments of up to $100 million for the MS indication, which is contingent upon completion of R&D, successful commercialization, and meeting certain sales milestones, and bears inherent risks as does all pharmaceutical R&D. Teva would fund and perform all future development of ATL1102 beyond the current trial should it decide to continue beyond that point. If ANP fails to meet a particular development milestone regarding completion of the current ongoing, fully enrolled Phase IIa study by the agreed date in mid 2008, Teva may terminate the agreement and receive a $2 million termination fee. Royalties are payable on net sales of ATL1102 are in the low double digit range and are tiered according to annual net sales achieved. The agreement also provides an option for Teva to in-license ATL1102 as an aerosol drug for asthma.

Under a separate collaboration and license agreement between ANP and Isis Pharmaceuticals Inc., ANP pays Isis one third of sublicense fees and milestone payments received from Teva, as well as a percentage of any royalties ANP receives.

“We are delighted to have signed this significant licensing deal with one of the world's leading pharmaceutical companies. Clinical stage deals such as this are subject to very stringent selection criteria, and we are particularly pleased that Teva has recognized the drug's commercial potential. Teva is a company with tremendous expertise in developing drugs, and is our partner of choice,” said ANP’s Managing Director, Mark Diamond.

ANP will continue to manage and fund the current Phase IIa clinical trial in relapsing-remitting MS patients, which is on track for completion of dosing, unblinding of the clinical trial, and reporting of results in mid 2008.

ATL1102 is a second-generation antisense inhibitor of CD49d, a subunit of VLA-4 (Very Late Antigen-4), and is currently in Phase IIa clinical trials as a treatment for MS. In inflammation, white blood cells (leukocytes) move out of the bloodstream into the inflamed tissue, for example, the CNS in MS, and the lung airways in asthma. The inhibition of VLA-4 may prevent white blood cells from entering sites of inflammation, thereby halting progression of the disease. VLA-4 is a clinically validated target in the treatment of MS. Antisense inhibition of VLA-4 has demonstrated positive effects in a number of animal models of inflammatory disease, including MS.

Market News and Trends

EUSA Pharma Out-Licenses Preclinical-Stage Human Antibody to GlaxoSmithKline for up to $44 Million Plus Royalties

EUSA Pharma, Inc., a transatlantic specialty pharmaceutical company focused on oncology, pain control, and critical care, recently announced it has out-licensed the exclusive worldwide rights to its preclinical-stage human anti-interleukin-6 antibody to GlaxoSmithKline (GSK) for a consideration of up to $44 million, comprising an up-front fee and development milestones, plus royalties on future sales. As part of the agreement, EUSA will pay approximately 50% of the overall consideration to its development partner for the antibody, Vaccinex Inc. GSK will fund and conduct all future development, production, and commercialization of the product.

Interleukin-6 is a pro-inflammatory cytokine and B-cell growth factor and acts as a resistance factor to standard chemotherapy. EUSA's product, OP-R003, is the first fully human anti-interleukin-6 antibody, with target indications in oncology and inflammatory diseases. OP-R003 is derived from a first-generation murine antibody, elsilimomab, which has achieved promising clinical results as a lymphoma therapy. As a fully human antibody, OP-R003 has the potential to offer improved tolerability and a superior safety profile.

EUSA acquired OP-R003 as part of the company's 2007 acquisition of OPi SA. OPi had previously entered a collaboration with Vaccinex, a specialist antibody discovery and development company, to optimize and develop OP-R003 as a therapy for rheumatoid arthritis and lymphoma.

"The out-licensing of this early stage antibody is another strategic milestone for EUSA, as we continue to focus our business on marketed and late-stage products in the oncology, pain control, and critical care areas," said Bryan Morton, Chief Executive of EUSA Pharma.

"Interleukin-6 is increasingly recognized as an important biological target in a range of diseases, and consequently OP-R003 has great potential to meet a number of unmet medical needs," added Brian McVeigh, GSK's Worldwide Business Development Director of M&A Strategy and Transactions.

EUSA Pharma is a rapidly growing transatlantic specialty pharmaceutical company focused on in-licensing, developing, and marketing late-stage oncology, pain control, and critical care products. The company currently has six products on the market, including the antibiotic surgical implant Collatamp G, Erwinase, and Kidrolase for the treatment of acute lymphoblastic leukemia, and Rapydan, a rapid-onset anesthetic patch that received Europe-wide approval in late 2007. EUSA also has several products in late-stage development, notably Collatamp G topical, a gentamicin impregnated collagen sponge for the prevention and treatment of infected skin ulcers, and CollaRx bupivacaine implant for local post-surgical pain control. Founded in 2006, EUSA Pharma is supported by a consortium of leading life science capital investors, comprising Essex Woodlands, 3i, Goldman Sachs, Advent Venture Partners, SV Life Sciences, NeoMed, and NovaQuest. Since its founding, the company has raised over $225 million and completed several significant transactions, including the acquisitions of Talisker Pharma Ltd, the French biopharmaceutical company OPi SA, and the European antibiotic and pain control business of Innocoll Pharmaceuticals Inc. As part of its rapid growth strategy, the company has established commercial infrastructure in the US, a pan-European presence covering over 20 countries, and a wider distribution network in a further 25 territories. EUSA Pharma plans to continue its aggressive program of acquisitions and in-licensing within its specialist areas of medical and geographic focus, in line with its ambitious target to create a rapidly growing $1-billion company by the beginning of the next decade.

DSM Announces Manufacturing Agreement, Change in Management

DSM Pharmaceuticals, Inc., a business unit of DSM Pharmaceutical Products, and APT Pharmaceuticals, Inc. recently announced they have signed a manufacturing agreement. DSM will produce the commercial drug supply as a sterile product for pulmonary delivery for APT Pharmaceuticals. The agreement will utilize DSM's commercial facilities in Greenville, NC.

"DSM has a superior reputation in sterile manufacturing, experience with similar drug products, and an excellent working relationship with the FDA," said Howard Raff, PhD, COO, APT Pharmaceuticals, Inc. "In addition to their experience, they also have the capability to provide increased scale through commercialization."

"DSM Pharmaceuticals Inc. is pleased to welcome APT as a client. APT is a specialty drug development company with an outstanding staff that is focused on effective treatments for significant unmet medical needs, and we at DSM are proud to be part of those efforts." added Terry Novak, President, DSM Pharmaceuticals Inc.

APT Pharmaceuticals, a specialty drug development company primarily focused on inhaled treatments for serious lung diseases, is based in Burlingame, CA. APT is backed by several leading healthcare investors including Vivo Ventures, Versant Ventures, Great Point Partners, and Charter Life Sciences.

DSM Pharmaceuticals, Inc. also announced that Dr. Hans Engels has been appointed to the position of President and Business Unit Director of DSM Pharmaceuticals Inc. Mr. Engels will continue to be based out of the Greenville, NC facility. Dr. Engels joined DSM in 2000, and most recently served as the Chief Operating Officer, DSM Pharmaceutical Products. During his 8 years experience with DSM, he has also been the Chief Operating Officer and Site Director for DSM Pharmaceuticals Inc. Prior to joining DSM in 1999, he was the Vice President of Production and Engineering for Alpha Therapeutics and has held various Executive Leadership positions for Bayer AG. Dr. Engels holds a BS in Mechanical Engineering from the University of Dusseldorf in Germany, and an MS and PhD in Chemical Engineering from the University of Aachen in Germany.

Market News and Trends

Pfizer to Acquire Encysive Pharmaceuticals & Thelin Lung Drug

Pfizer Inc. recently announced it has entered into an agreement to acquire Encysive Pharmaceuticals Inc., a publicly held biopharmaceutical company whose product for the treatment of pulmonary arterial hypertension (PAH) is commercially available in much of the European Union and is approved in other markets.

Under the terms of the agreement, Pfizer will make a cash tender offer for all issued and outstanding shares of Encysive for $2.35 per share, representing an equity value of approximately $195 million. Following completion of the tender offer, a subsidiary of Pfizer will merge with Encysive, with the outstanding Encysive shares not tendered pursuant to the tender offer converted into the right to receive the per share price paid under the offer. Upon Pfizer's acquisition of Encysive, Pfizer will assume Encysive's change of control repurchase obligations under its 2.5% convertible senior notes. The Board of Directors of Encysive has unanimously approved the merger agreement and unanimously recommends that Encysive stockholders accept the tender offer and tender their shares.

Pfizer will acquire the rights to Thelin (sitaxsentan sodium), an oral, once-daily endothelin A receptor antagonist (ETRA) for the treatment of PAH, as well as Encysive's other pipeline candidates. Thelin has been approved for marketing in the European Union (EU) and is currently available in many EU states, including the UK, Germany, Ireland, Spain, France, Italy, Belgium, Luxembourg, and the Netherlands. Thelin has also been approved in Australia and Canada. In the US, Thelin has been the subject of three approvable letters from the US FDA. Pfizer plans to conduct a pivotal Phase III trial to support registration in the US.

PAH is a progressive, incurable disease that is estimated to affect 100,000 to 200,000 people in North America and Europe, including about 55,000 people in the US. It may be idiopathic or secondary to other disorders, such as connective tissue disease. Though relatively rare, the disease affects men and women of all races and ages, but is more common among women aged 20 through 40. The disease may be misdiagnosed as asthma, anemia, or COPD. PAH is characterized by high blood pressure and structural changes in the walls of the pulmonary arteries. In PAH, the pulmonary arteries become thickened and constricted, forcing the heart to work harder to pump blood through the lungs. Over time, the heart is unable to keep up, and blood flow and oxygenation become inadequate to meet the body's demands. This can lead to breathlessness, fatigue, dizziness, fainting, edema, chest pain, and the development of heart failure.

Thelin works by blocking the action of endothelin-1, a potent mediator of blood vessel constriction. Thelin acts to dilate the constricted blood vessels, thereby reducing pulmonary arterial pressure and thus the demands on the right side of the heart, improving exercise tolerance.

The transaction is expected to close in the second quarter of 2008, subject to customary closing conditions, including approval under the Hart-Scott-Rodino Antitrust Improvements Act of 1976 and the acquisition by Pfizer of a majority of Encysive's shares in the tender offer. Lazard Frères and Co., LLC, and Weil, Gotshal & Manges LLP advised Pfizer on this transaction. Morgan Stanley and Covington & Burling LLP advised Encysive.

Market News and Trends

ICON Announces Acquisition of Healthcare Discoveries

ICON, a global provider of outsourced development services to the pharmaceutical, biotechnology, and medical device industries, recently announced it has acquired Healthcare Discoveries, Inc., a wholly owned subsidiary of Catalyst Pharma Group Inc. Under the terms of the agreement, ICON will pay an initial cash consideration of $12 million. If certain performance milestones are achieved in 2008, a further consideration of up to a maximum of $10 million may be payable. Healthcare Discoveries operates an 85-bed clinical pharmacology unit in San Antonio, TX, and has significant experience of delivering high-quality early phase development programs.

"The acquisition of Healthcare Discoveries is an important step for ICON," said ICON CEO Peter Gray. "It gives us a clinical pharmacology platform in the US to complement our existing European Phase I operations. As well as gaining an outstanding facility, we are bringing into ICON an experienced team that has an excellent market reputation."

Healthcare Discoveries will become part of a comprehensive early phase development portfolio within the ICON Development Solutions division, which includes an existing 80-bed clinical pharmacology unit based in Manchester, England.

"The investment in Healthcare Discoveries will enable us to meet the growing demand for highly scientific first-in-human and full-spectrum clinical pharmacology studies that are a critical part of the drug development process," said Dr. Thomas Frey, President of this division. "We look forward to integrating these additional capabilities into our broad drug development service portfolio."

Dr. Richard Anthony, CEO of Catalyst Pharma Group, added, "We are delighted that Healthcare Discoveries will become part of the ICON group. Catalyst has worked with Dr. Dennis Ruff, President of Healthcare Discoveries, for the past 4 years to build a reputation for excellence in Phase I research. We believe ICON's early phase development experience, focus on quality, and business culture is an ideal fit with Healthcare Discoveries. Catalyst looks forward to continuing to work with Healthcare Discoveries in the future."

ICON plc is a global provider of outsourced development services to the pharmaceutical, biotechnology, and medical device industries. The company specializes in the strategic development, management, and analysis of programs that support clinical development (from compound selection to Phase I-IV clinical studies). ICON teams have successfully conducted over 1,900 development projects and over 2,300 consultancy engagements across all major therapeutic areas. ICON currently has approximately 5,600 employees, operating from 67 locations in 35 countries.

Catalyst Pharma Group Inc. was formed specifically to meet the needs of companies with limited US presence that are seeking to develop, approve, and market pharmaceuticals in the US. CPG is a drug development services organization specializing in providing contiguous, integrated, cost-effective drug development solutions through internal divisions and the combined services of its partnered companies.

Novozymes & Upperton Collaborate on Novel Nanoparticle Drug Technology

Novozymes recently announced a new collaboration agreement with Upperton Limited, a UK-based biotech company specializing in novel nanoparticle-based drug delivery systems. The agreement extends previous collaborations between the two companies and will focus on the commercial exploitation of the jointly owned rP-nano technology, a highly targeted drug delivery system that utilizes the natural binding properties of recombinant protein nanoparticles to enhance drug and gene bioavailability.

Under the terms of the agreement, Upperton will use rP-nano technology to generate nanoparticles from recombinant proteins expressed in Novozymes' proprietary, yeast-based expression system. Uniquely, rP-nano technology can generate precisely sized nanoparticles within the range of 10 nm to 120 nm and can be optimized for enhanced permeability and retention effect. The nanoparticles produced through this process retain the natural binding properties of the recombinant proteins from which they are made, and bind to specific cell types to enable more targeted drug delivery and improved bioavailability.

"I am extremely pleased to be continuing our collaboration with Novozymes," said Richard Johnson, MD, of Upperton Limited. "Use of their animal-free, GMP recombinant proteins will be extremely important as we look to commercialize our unique technology. In addition, Novozymes' regulatory knowledge and expertise in yeast-based protein expression will allow us to faster develop rP-nano technology and create a very attractive proposition for future marketing or licensing partners."

"Our original research demonstrated the huge potential of rP-nano technology, and we are very pleased to continue collaborating with Upperton to develop this further," added Dr. Dave Mead, Novozymes' UK-based Business Development Director. "This is further exemplification of Novozymes' high-yielding expression systems being used for the production of pharmaceutical-grade recombinant proteins."

rP-nano technology can produce nanoparticles from all peptides and proteins, including monoclonal antibodies and enzymes, without denaturation. The suitability of this technology to pharmaceutical applications will be demonstrated to potential licensees through nanoparticles generated from recombinant human albumin. Novozymes is the sole manufacturer of the worlds' only animal-free commercially available recombinant human albumin approved for use by the EMEA and FDA in the manufacture of human therapeutics, Recombumin. For proof-of-principle, Upperton has loaded Novozymes' recombinant human albumin with monoclonal antibodies, radioactive metal ions, chemotherapeutic agents, and paramagnetic metal ions.

Upperton Limited, founded in 1999, is a privately owned biotech company based in Nottingham, UK, and specializing in spray drying and particle technologies. They have recently co-patented rP-nano technology with Novozymes as a next-generation technology for producing nano-sized particles from proteins with broad application. The rP-nano technology offers unique competitive advantages over current methods of producing nanoparticles. Upperton welcomes academic and industrial partners to explore and commercialize this technology.

Novozymes' products, with over 700 used in 130 countries, improve industrial performance and safeguard the world's resources by offering superior and sustainable solutions for tomorrow's ever-changing marketplace. Novozymes' natural solutions enhance and promote everything from removing trans-fats in food to advancing biofuels to power the world tomorrow.

Cellegy Pharmaceuticals Announces Signing of Definitive Merger Agreement

Cellegy Pharmaceuticals, Inc. recently announced it has entered into a definitive merger agreement providing for the acquisition of Cellegy by Adamis Pharmaceuticals Corporation. Adamis is a privately held specialty pharmaceuticals company that is engaged in the research, development, and commercialization of products for the prevention of viral infections, including influenza. Adamis currently markets and sells a line of prescription products for a variety of allergy, respiratory disease, and pediatric conditions, and also owns a GMP-certified independent contract packager of pharmaceutical and nutraceutical products. Adamis' CEO, Dr. Dennis Carlo, is expected to become the CEO of the combined company. Dr. Carlo is a veteran of the pharmaceutical and biotechnology industry, having previously served as CEO of publicly traded Immune Response Corporation, President of Telos Pharmaceuticals, and Vice President of Research and Development and Therapeutic Manufacturing of Hybritech Inc. prior to its acquisition by Eli Lilly & Co.

The transaction was unanimously approved by the boards of directors of both companies and is anticipated to close during the second or third quarter of 2008, subject to the filing of a registration statement and proxy statement with the Securities and Exchange Commission, the approval of Adamis' and Cellegy's respective stockholders at stockholder meetings following distribution of a definitive proxy statement, and other customary closing conditions. Holders of approximately 40% of Cellegy's outstanding common stock have entered into voting agreements pursuant to which they agreed to vote their shares in favor of the transaction. The combined company expects to continue to be publicly traded after completion of the merger, although under a different corporate name.

"The merger of Cellegy and Adamis will create a new specialty pharmaceutical company focused on the development and commercialization of therapeutic products for a variety of viral diseases, including influenza," said Mr. Richard C. Williams, Cellegy's CEO. "We like the fact that in addition to technologies in development that we believe are promising, Adamis has allergy and respiratory products already being sold in the US marketplace, and a contract packaging company that provides a source of current revenue and the potential for future revenue and income growth."

"This merger allows us to fulfill our strategic objective of building a publicly traded company that combines biopharmaceutical research and development with the financial stability of a company producing immediate revenues from the sale of specialty pharmaceutical products and from the packaging of drugs for major pharmaceutical distributors. We believe the concept makes sense both financially and operationally," added Dr. Carlo.

Cellegy Pharmaceuticals is a specialty biopharmaceutical company that specializes in women's health. Savvy (C31G vaginal gel), a microbicide gel product for contraception, is currently undergoing Phase III clinical studies in the US for contraception.

Adamis is a specialty pharmaceutical company engaged in the research, development, and commercialization of prescription medicines for the treatment of viral infections, including influenza. Adamis also markets several prescription allergy and respiratory products in the US and is developing additional product candidates in the allergy and respiratory field. Adamis also owns a specialty packaging company that provides packaging for pharmaceutical and nutraceutical products.

Ocera Therapeutics Closes $35.5-Million Series C Financing

Ocera Therapeutics, a biopharmaceutical company focused on the licensing, development, and commercialization of proprietary compounds to treat a broad range of gastrointestinal and liver diseases, recently announced the completion of a $35.5-million Series C financing from a syndicate of highly-regarded investors.

New investor Montagu Newhall Associates is leading the round and is joined by InterWest Partners; AgeChem Venture Fund; Cross Creek Capital, an affiliate of Wasatch Advisors; FinTech; and CDIB BioScience. Previous investors, Domain Associates, Sofinnova Ventures, and Thomas, McNerney & Partners, also participated in the round.

To date, Ocera has raised a total of $62 million. In conjunction with the financing, Linda Grais of InterWest Partners will take a seat on the Ocera Board of Directors, representing Montagu Newhall Associates and the Series C investors.

"I am extremely pleased with the investor confidence we've seen from this oversubscribed financing round," said Laurent Fischer, MD, Co-founder, President, and CEO of Ocera Therapeutics. "We are privileged to have attracted a syndicate of renowned investors with specific expertise in the gastrointestinal market as well as international and crossover investors, and we welcome Linda Grais' guidance as she joins our Board of Directors."

"Ocera Therapeutics is a unique biopharmaceutical company, which has achieved bringing AST-120 through Phase III trials for Crohn's disease in a very short time and in a capital efficient manner," said Ashton Newhall, General Partner, Montagu Newhall Associates. "Our confidence in the ability of Ocera's management team to deliver on its goals and expand the market opportunity for this product by focusing on orphan drugs as well as other indications with unmet medical needs makes this an exciting opportunity. We look forward to upcoming milestones related to AST-120."

AST-120 Spherical Adsorbent Carbon is not absorbed in the body. It was in-licensed in 2005 from Kureha of Japan. Ocera has completed enrollment in FHAST1, the Fistula Healing with AST-120 Phase III pivotal trial in Fistulizing Crohn's disease conducted in North America, Europe, and Israel. Ocera is studying AST-120 in a Phase II trial for Pouchitis, an orphan drug indication, and has also initiated proof-of-concept trials in Irritable Bowel Syndrome, Hepatic Encephalopathy, and PPI-resistant GERD.

Azopharma Product Development Group Opens Cyanta Analytical Laboratories Facility

Azopharma recently announced the opening of a new Cyanta Analytical Laboratories facility in Maryland Heights, MO. The new 20,000-sq-ft modern laboratory is equipped with state-of-the-art instrumentation to support pharmaceutical and medical device product development, specifically analytical method development and inhalation/respiratory services.

"With the opening of our new facility, Cyanta becomes the center of excellence for all analytical support in the inhalation industry," said CEO, Phil Meeks. "This facility allows us to continue to provide industry-leading quality services that Cyanta is already known for. The new facilities have been modified and updated to meet the stringent demands of our pharmaceutical, medical device, and biotech customers, and we will continue to adapt to meet their growing demands as necessary."

The newest instrumentation additions include Anderson and next-generation impactors for aerodynamic particle sizing, Proveris SprayView Unit, Malvern SprayTech, walk-in stability chambers with standard ICH conditions, custom stability chambers that provide various temperatures and humidity conditions, stability and laboratory areas monitored by the Kaye LabWatch System, state-of-the-art GC/MS and LC/MS (Triple Quad, Ion Trap, Tandem MS, MSn) for structural characterization and elucidation, and gel permeation chromatography instrumentation.

Cyanta Analytical Laboratories provides analytical services to the pharmaceutical, biotech, and medical device industries. As part of the Azopharma Product Development Group, Cyanta's services focus on stand-alone analytical projects for pharmaceutical products and medical devices, whether in development or currently marketed. Cyanta services support early to late-phase projects, including analytical development, method validation, stability testing, extractables and leachables, inhalation development services, and analytical support for formulations. Cyanta Analytical Laboratories along with the Azopharma Product Development Group of companies provides a complete spectrum of product development services for the pharmaceutical, medical device, and biotech industries.

The company's capabilities and services include Azopharma Contract Pharmaceutical Services (integrated product development and CTM manufacturing for all dosage forms), ApiCross Drug Delivery Technologies (proprietary drug delivery platforms to solve difficult molecular challenges), Cyanta Analytical Laboratories (analytical chemistry and inhalation services from development to quality control testing), AniClin Preclinical Services (preclinical services in support of early product development), IQsynthesis (synthetic chemistry services from discovery to clinical API supplies including large-scale API synthesis), and AvivoClin Clinical Services (human clinical pharmacology services for Phase I/II/III clinical trials).

"Azopharma Product Development Group is only one of a few organizations in the US that are capable of developing a full spectrum of dosage forms from discovery through clinical trial manufacturing," added Mr. Meeks. "By bringing together the best scientists in the field, state-of-the-art facilities, and our focus on quality, means that we can provide our partners a winning combination in product development. All Azopharma PGO facilities are FDA registered and inspected, DEA approved, and client audited on a regular basis."

Market News and Trends

Gerresheimer Takeovers, Acquisitions Lead to Increasing Global Presence & Record Year

Gerresheimer AG, according to provisional figures, has reported another record year. In 2007, the company achieved sales of $1.3 billion (up by 48.1%), and the adjusted Group EBITDA margin reached 19%. “This gratifying development completely and fully confirms our strategy,” says Dr. Axel Herberg, Chief Executive Officer of Gerresheimer AG. “With the help of acquisitions, we have successfully expanded our global presence and set the course for further growth.”

Shortly after taking over EDP S.A., the Spanish market leader for pharmaceutical PET bottles with production plants in Spain (Zaragoza and Valencia) and South America (Buenos Aires, Argentina), this international company, based in Düsseldorf, Germany, also announced the acquisition of Allplas Embalagens Ltda. (São Paulo), which is the market leader for pharmaceutical plastic packaging in Brazil. This marks the successful completion of another important step in the global expansion of the Gerresheimer Group.

For Gerresheimer’s Plastic Systems Division, finalization of the latest contract puts the cap on a dramatic move into South America. It was only at the end of December 2007 that Gerresheimer acquired EDP, thereby also establishing a foothold in South America for the first time. EDP currently achieves annual sales of an estimated $44 million. With Allplas, which operates two production plants in São Paulo, Gerresheimer now already has three strategically important bases in the region.

Allplas manufactures high-calibre vials and application and closure systems for liquid formulations and solid dosages (eg, drops and tablets), which ideally complement (and can be combined with) Gerresheimer’s product range. The Group’s existing product portfolio in the field of plastic packaging, which has so far been marketed primarily in Europe, will as a result increasingly find its way into the South American pharmaceutical markets. Allplas currently achieves annual sales of around $22 million. Like EDP, Allplas will become part of Gerresheimer Plastic Packaging, which specializes in pharmaceutical primary packaging and application systems under leading trade¬marks, such as Duma®, Dudek™ and EDP™.

Together with the two acquisitions, Gerresheimer’s plastic operations achieve a total annual sales volume of around $477 million, $136 million of which is attribut¬able to the plastic packaging segment.

Gerresheimer employs more than 10,800 people in 40 locations in Europe, America, and Asia. Its product portfolio ranges from pharmaceutical vials made of glass and plastic to complex drug delivery systems for the pharma and life science industry. These include sterile syringes, inhalers, and other system solutions for secure dosage and application of medications. Gerresheimer’s products are subject to extremely rigorous quality requirements stipulated by the international pharmaceutical supervision authorities.

What is the Value of Your Company?

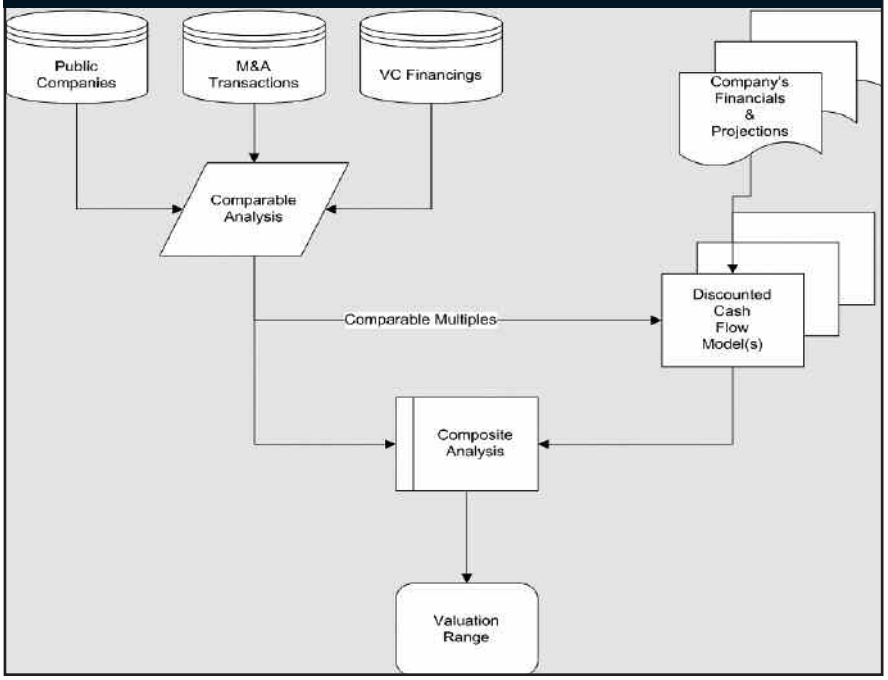
By: Tim Howard, MBA, and Debra Bingham

It is the simplest and most important question in business, "Would you be willing to sell your company?" In most cases, your response will most likely be, "It depends, what would you be willing to pay?" If you are lucky enough to get an answer in such an exchange from a qualified acquirer, it is imperative to understand what is the underlying value of your enterprise. Is the acquirer talking about a discount, premium, or market price for my enterprise?

As a senior executive in a publicly traded life sciences company, you can find the value of your firm by going to one of dozens (if not hundreds) of financial websites and entering your stock ticker symbol. As a Founder/CEO of a private drug delivery or specialty pharmaceutical company, the question is not so easily answered. If your company has adopted a periodic valuation process to ensure stock option grants are in compliance with recent IRS regulations (see Side Bar – Implications of IRC 409A), you should have a recent valuation report to use as a starting point for the question. If your company has not yet adopted such a process, adopting one may be an investment to strongly consider. The remainder of this discussion will outline a valuation approach often used in M&A situations.

A standard enterprise valuation methodology will often utilize multiple components. Note that this analysis focuses on the Enterprise Value, not the Market Value of a company. Enterprise Value is used to eliminate the impact of financing decisions on the valuation process. Weighting factors are applied to each component based upon their respective relevance and reliability. The components that are utilized are relatively standard, and will be discussed in the further sections below. It is the weighting of the different components based upon the unique circumstances of your company that determine the precision of the resulting valuation range.

FIGURE 1



COMPARABLE PUBLIC COMPANIES

Select publicly traded companies that operate in your sector. When examining comparable companies, it is important to assess valuation ratios that can be used for your business. Select a subset of companies that are similar to your company and that have available data such that you can generate reliable median and narrow average valuation multiples.

The median and narrow average (similar to the mean with the exception of eliminating the highest and lowest value of the set in the calculation) often provide more reliable estimates than a pure average as the impact of outliers is minimized. Ideally, if the comparable set has adequate data to support the generation of EV/EBITDA and EV/Earnings ratios (the aforementioned example set did not have sufficient EBITDA or earnings in 1Q2007), these can be used for generating multiple comparisons for profitable private firms. It is often most applicable to utilize Enterprise Value (EV)/Revenue ratios if your firm has not achieved profitability.

When looking at public company multiples, it is common practice to discount such multiples (by up to as

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much as 30%) to account for the liquidity value of public listings. Caution is advised in applying such a discount if the company is contemplating an M&A transaction, as such a situation will place a premium on control of the enterprise that will often offset the private company liquidity discount.

RECENT M&A TRANSACTIONS & VENTURE FINANCINGS

Generate a list of recent M&A transactions that have occurred in your sector. You will be limited to the publicly announced information on the transaction, often again limiting you to a multiple of trailing revenue. When examining comparable transactions, the timeliness of the transaction must be considered, and aged transactions require justification for inclusion. We would recommend limiting comparable transactions to the most recent 12-month period.

Recent venture financings in the sector can also be examined. In most cases, revenue or earnings multiples will not be available, and you will be limited to examine pre- and post-money valuations. Once again, it will be important to work to identify those companies that are most comparable (stage of enterprise, funding to date, profitability).

COMPANY PROJECTIONS & HISTORICAL TRANSACTIONS

The heart of a company valuation is anchored in the management-provided financial projections. These projections are utilized to generate a discounted cash flow model that projects the value of the firm over future periods. The cash flow model should reflect the anticipated timeframe to a liquidity event. An exit value needs to be calculated at that point (often based upon public company multiples). One of the key components of the model is a discount rate that adequately accommodates the company's cost of capital and the uncertainty associated with the projections. The end result is a net present value of the enterprise today, based upon management's current view of the future. It must be noted that it is possible that the near-term management projections exclude additional revenues that may be garnered from the underlying technology if it were in the hands of a better funded entity. In such instances, it is necessary to include a technology valuation component along with the discounted cash-flow model (see Technology Valuation section further on).

If the company has had one or more recent arms-length transactions (such as a Series-A venture round), it is useful to do an incremental analysis of the value change in the company from the time of the transaction. For example, if trailing 12-month revenue has increased by X%, the company has turned the corner on profitability, or the client base has increased Y%, one could apply these changes to the post-money valuation of the last financing round.

Keep in mind that there may be multiple variants of the discounted cash-flow model and the recent transactions. For example, with the DCF, you may have multiple scenarios and/or want to utilize EV/Revenue or EV/Earnings multiples to calculate the terminal value.

IMPLICATIONS OF IRC 409A

The historic practice by emerging growth companies to often use stock options as a method to attract, retain, and motivate key employees has recently taken on new complexities and potential liabilities. Changes to the Internal Revenue Code (ie, final 409A Regulations issued in April, scheduled to become effective starting in 2008) state deferrals of compensation under a non-qualified deferred compensation plan for all taxable years are currently includible in gross income to the extent they are not subject to a substantial risk of forfeiture and not previously included in gross income, unless certain requirements are met. To ensure that Incentive Stock Options (ISOs) and non-qualified stock options (NSOs) are not subject to Section 409A, it is imperative they be issued with an exercise price of not less than fair market value (FMV) on the date of grant. For companies that do not have publicly traded stock, any "reasonable valuation method" may be used for purposes of determining the FMV of the stock at the date of grant. To meet this standard, it is not necessary that a firm use an independent appraiser; however, the final regulations adopt a presumption in specified circumstances that, for purposes of section 409A, the valuation is considered reasonable if performed by an independent appraiser unless the IRS can show it is grossly unreasonable. The impact of Section 409A non-compliance is significant, as penalties for inadequate withholding can rapidly accumulate, and the positive incentive associated with stock options can quickly be eliminated if employees are saddled with a current tax liability and no guarantee of a future pay-out. Additionally, clean-up of 409A related issues can potentially delay audits, funding, and liquidity events. Visit www.irs.gov for more information on the guidance regarding reasonable valuation methods. It is recommended you consult your tax advisor on the impact of IRC 409A to your business.

TECHNOLOGY VALUATION

Specialty pharma and drug delivery companies are typically technology rich companies. As part of management's financial projections, a technology valuation will be performed. The technology is sometimes more difficult to evaluate from a market perspective than are pipeline products. An underlying platform technology, be it drug delivery or other technology, may be vital to the company but will not be as highly valued as its pipeline products. The management team must take a realistic look at the many applications of the internal technology and determine a market value. The foundation of the technology valuation process is the assumptions used, including potential technology applications, time to market, cost of development, chance of success, peak sales/market share, and competition. Solid assumptions and a realistic discount factor are essential to combat the push-back on valuation that will take place during

negotiations. It is important to do the homework to assure that your assumptions regarding market potential and competition are as bullet-proof as possible. This will lend important credibility to the other pieces of the company valuation.

BRINGING IT ALL TOGETHER

The last step in the process brings together all of the components; and you are faced with the prospect of weighting each component in the generation of a composite valuation range. Ultimately, the weights are determined by the sample size and how close the public company and transactions compare with your enterprise and how confident you are with the future management projections. The composite table might look like the following

FIGURE 2

($000s)	Upper Estimate	Lower Estimate	Weighting
Comparable Public Companies (Revenue)	$ 55,000	$ 47,000	10%
Comparable Public Companies (EBITDA)	$ 52,000	$ 49,000	10%
Comparable Public Companies (Earnings)	$ 60,000	$ 45,000	10%
Comparable M&A Transactions (Revenue)	$ 69,000	$ 51,000	10%
Comparable M&A Transactions (EBITDA)	$ 58,000	$ 54,000	10%
Discounted Cash Flow (Revenue)	$ 60,000	$ 52,000	20%
Discounted Cash Flow (EBITDA)	$ 66,000	$ 60,000	20%
Discounted Cash Flow (Earnings)	$ 72,000	$ 68,000	10%
Weighted Average Valuation	$ 61,500	$ 53,250	100%

It is important to perform a sensitivity analysis to determine what two or three factors drive the valuation and ensure that assumptions associated with these factors are validated. Once completed, you should end up with a valuation range that can be utilized in the pricing of stock option grants. As noted in the side bar, it is imperative that stock options be priced at or above fair market value to avoid IRC 409A treatment. If performed on a regular basis, the approach outlined herein will allow you to monitor the value of your enterprise, taking into account changes in the market (public companies and transactions) and the progress made by your team (management projections). ◆

AUTHORS' NOTE

The valuation method described herein is focused on enterprise value. It must be noted that FASB Statement 123 (Revised) requirement to measure stock option expense requires additional analysis, potentially utilizing a Black-Scholes or binomial (lattice) model that is beyond the scope of this article.

BIOGRAPHIES

Mr. Tim Howard leads the Healthcare Practice at Stonecroft Capital, a boutique investment banking firm specializing in mergers and acquisitions and commercialization activities. Mr. Howard has over 20 years of entrepreneurial, management, and transaction experience in the Healthcare and Technology sectors. He has led venture financing, partnering and acquisition activities, and negotiated strategic transactions with global pharmaceutical and medical device firms, including Pfizer, GlaxoSmithKline, Johnson & Johnson, Baxter, Eli Lilly, Sanofi-Aventis, Amgen, Genentech, Biogen Idec, Gilead, Schering-Plough, Schering AG, Solvay, Bayer, Otsuka, Surmodics, Smith & Nephew, and AmerisourceBergen. Prior to joining Stonecroft Capital, Mr. Howard was CEO of Galt Associates, a bioinformatics firm he founded, that provided solutions to leading biopharmaceutical and medical device companies worldwide and was subsequently sold to Cerner Corporation. During his tenure as CEO, Mr. Howard was twice selected as an Ernst & Young Entrepreneur of the Year Finalist in the life sciences sector, and twice led Galt to positions in the Deloitte & Touche National Fast 500 and Virginia Fast 50. Mr. Howard's education includes a BS in Physics and Mathematics from Ursinus College, and an MBA from The Wharton School of the University of Pennsylvania.

Ms. Debra Bingham is a Partner of Valeo Partners, a Washington, DC-based firm that provides strategic consulting, business development, and M&A services to life science companies in the pharmaceutical, biotechnology, medical device, and drug delivery markets. Ms. Bingham brings clients over 14 years of specialized expertise in the pharmaceutical and drug delivery industries. Her clients include large multi-national pharmaceutical and chemical companies as well as medium-to-small specialty pharma and drug delivery companies. As part of her consulting career, she spent more than a decade working directly with North American, European, and Japanese companies in the area of business development strategy and licensing. Her uniquely strong network in Japan, Europe, and North America has been an asset to her clients. Her primary focus is directing companies in the areas of partnering, business strategy, and growth opportunity assessment.

Understanding the Regulatory Environment for Combination Products in the World's Leading Markets

By: Christine M. Ford, MBA

While combination products promise to deliver novel treatment where traditional pharmaceutical drugs have failed or are less effective, development of these innovations pose unique challenges on the road to approval and commercialization. To help overcome these challenges, several countries are working to harmonize and better define the regulatory process for combination products. This article focuses on the regulatory initiatives of the US, Japan, and the European Union (EU). As the primary driver of regulatory initiatives for combination products, the US has created a regulatory framework for other countries to emulate, particularly Japan.

DEFINING THE REGULATORY PROCESS

The complexity of this product development paradigm is evidenced by the fact that the FDA created the Office of Combination Products (OCP) in 2002 specifically to oversee the approval process, safety, and accountability of combination products. The OCP's main purpose is to assign primary jurisdiction to an FDA center for review of a combination product. Essentially, the OCP functions as a central body that helps identify the component parts of new product applications to ensure that the appropriate divisions are reviewing respective elements.

Combination product developers seeking to gain approval in the US have a much simpler road ahead than their European counterparts, as there is no European equivalent of the OCP. Primary Mode of Action (PMOA), the rule governing assignment of a new combination product to one of the three FDA regulatory centers for review - the Center for Biologics Evaluation and Research (CBER), Center for Drug Evaluation and Research (CDER), and the Center for Devices and Radiological Health (CDRH) - ensures that combination products are reviewed by the most appropriate center. What makes the FDA's approach so unique is the intercommunication that takes place between the OCP and its three regulatory centers. While one center may have primary jurisdiction over a product, other centers participate in the review to ensure that all component parts are effectively evaluated.

APPROVAL CHALLENGES ABROAD

Because the European Union (EU) does not provide separate channels for the approval of combination products, they are regulated almost solely on the manufacturer's intended claims for the product. For example, a wound-care product containing an antimicrobial can be considered a device if the antimicrobial is there to help prevent excessive odor, but it will be regulated as a pharmaceutical if the claim is to treat or prevent infection. There are other situations in which the manufacturer largely determines the classification, such as bone cements with antimicrobials.

Another challenge of combination product approvals in the EU is that each country has its own authorities to handle approval of combination products, and each operates on its own timetable. This means that a combination product will typically have an unpredictable road ahead for regulatory approval in each EU country.

THE EU REVIEW PROCESS

Unlike pharmaceutical products, placing medical devices on the market in Europe is not subject to a formal authorization. Devices are classified based on a number of rules described in the Medical Devices Directive (MDD), which builds on the concept of a risk-based approach related to the device's duration of use, invasiveness, and associated hazards. Different combinations are regulated differently according to the European Commission's classifications. Combination products generally fall into Class III devices, which present the highest risks and are subject to the most stringent assessment and third-party certification.

A device that is intended to deliver a medicinal product is itself regulated as a medical device. The medicinal product that the device is intended to administer must be approved according to the normal procedures for medicinal products. Some examples include drug delivery pumps, implantable infusion pumps, and nebulizers. Note that in a kit comprising an insulin pen and insulin cartridges, the pen is subjected to device approval, but the insulin cartridge is considered a medicinal product.

If the device and medicinal product form a single, integral product that is intended exclusively for single use in the given combination, then that single product is regulated as a medicinal product. Examples of such products include prefilled syringes, transdermal patches, and various implants, such as plastic beads with antimicrobials for bone infections.

In general, EU authorization (CE marking) for medical devices is deemed easier to obtain than FDA approval. This is mainly because the European Commission is mainly concerned with safety, therefore, clinical efficacy requirements are not necessarily as rigorous as those in the US. Companies can usually get their medical devices on the market faster in Europe than in the US, although for drug-device combinations, the EU pharmaceutical regulatory bodies will scrutinize the drug portion as thoroughly as the FDA would.

APPROVALS IN THE US VERSUS THE EU

While EU combination product approvals may be faster than FDA approvals, the size of the domestic healthcare market, coupled with the weight US approvals carry abroad, makes a compelling case for commercializing combination products in the

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US first. In addition, the FDA's well-defined path to approval makes review simpler, even though it is not necessarily faster. These advancements are reflected in the fact that the US leads the combination product market with a 65% market share followed by Europe and then Japan.[1,2]

Conversely, a combination product approved first in the EU can influence the FDA review process in a positive way. While the FDA is in no way bound by the decision of any other regulatory body, the rationale used to reach that decision may be informative for the FDA. However, some products the FDA would regulate as a drug or biological the EU might deem to be solely a device, in which case, the review process would not be as stringent, and would therefore not carry the weight of a pharmaceutical approval. In other words, different regulatory bodies operate according to different definitions of medical devices, pharmaceutical products, and biologics, so the impact of these other decisions is not direct.

While the EU and US regulatory bodies are independent bodies that make decisions based on their respective criteria, conditions have improved for cross-regional cooperation in the past few years.

EYE ON JAPAN

As the largest medical device market in Asia, Japan plays an important role in the growth and advancement of combination products. Throughout the next few years, as Japan's economy continues to grow, imports of foreign medical devices are expected to increase by 5% to 8% annually and continue to represent 10% of the world market for medical devices.[3]

While gaining approval for a standard medical device or drug in Japan has been said to be a long and frustrating process, much of this depends on the level of trust the product developer has established with Japan's Ministry of Health, Labor, and Welfare (MHLW). A company's reputation and relationship with the MHLW will greatly influence the speed with which products are reviewed and approved.

MHLW has established a structured means of classifying combination products for regulatory review. The MHLW defines combination products as a product consisted, composed, or combined of a drug and a medical device that is physically or chemically combined or co-packaged. However, the MHLW does not consider cross-labeled products to be combination products.

Like the US, a combination product is judged to be a drug or a medical device based on the primary mode of action of each product on case-by-case basis. Three divisions/offices of the MHLW are involved in such judgments, including the Licensing and Evaluation Division, the Medical Devices Evaluation Office, and the Compliance and Narcotics Division. If a product is judged to be a pharmaceutical, then the Office of New Drug of Pharmaceutical and Medical Devices Agency (PMDA) will lead the review. If the product is judged to be a medical device, then the Office of Medical Devices of the PMDA will head the review.

Although Japan has sought to emulate the US in terms of establishing the PMOA and assigning separate offices for the review of combination products, it lacks the intercommunication between offices that distinguishes the OCP from other regulatory bodies.

While drug-eluting stents are easily classified as a medical device and prefilled syringes are regulated as drugs, confusion does frequently arise with devices such as a drug-eluting contact lens. When this occurs, the various branches of the MHLW will decide the product's PMOA and appropriate review office.

MOVING TOWARD A HARMONIZED FUTURE

To ensure advancement of the combination products market, it is critical that regulatory standards keep pace with innovation. Driving these regulatory efforts are the Global Harmonization Task Force and the International Conference on Harmonization, which both focus on harmonizing methods of study, application, and product review. The former addresses medical devices and the latter focuses the pharmaceutical industry. The objective of these organizations is to reduce variations in regulatory pathways and expectations that are encountered by industry.

As the world's pioneer in regulatory advancement for the combination products market and chair country of the Global Harmonization Task Force, the US is helping to shape this dynamic industry. This, coupled with solid innovation capabilities, make the US a compelling place for multinational companies to develop and commercialize their combination products.

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BIOGRAPHY

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

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EXCIPIENT UPDATE

Bill Webb
Director of Quality, Eurand

Big Pharma & Suppliers Collaborate on Excipient Quality

Topic takes center stage at upcoming ExcipientFest® Americas conference

By: Cindy H. Dubin, Contributor

2006 in Panama: 21 people die after taking a government-made cough syrup contaminated with diethylene glycol that had been mislabeled as USP-grade glycerin, a widely used excipient. Another 38 people were affected by side effects, including disorientation and kidney failure.

1996 in Haiti: glycerine contaminated with diethylene glycol killed 88 people. 1990-1992 in India and Bangladesh: paracetamol (acetaminophen) syrup contaminated with diethylene glycol from propylene glycol led to 236 deaths. 1990 in Nigeria: 47 people die after taking cough syrup contaminated with solvents.

"In these cases, the fraud was deliberate; the material was mislabeled for pharmaceutical use," says Chris Moreton, PhD, a Partner with FinnBrit Consulting in Waltham, MA. "The people accepted the material on the basis of a certificate of analysis (CoA). The ID test in both 1996 and 2006 may not have picked it up. The FDA has since mandated changes, and there is now a test for absence of DEG in the USP monograph for glycerin."

Dr. Moreton, who will present *Excipient Sourcing in a Global Market: How to Avoid Another Panama* at the upcoming ExcipientFest® Americas annual conference and pharmaceutical expo in Puerto Rico (April 16-18), believes events such as the aforementioned are not just happening in developing countries. He will discuss what is being done to make it more difficult for these incidents to occur. Earlier in 2007, several countries (including the US) issued a major recall of toothpaste made in China because it contained diethylene glycol that had again been mislabeled as glycerine.

"Situations like this are not widespread, but it is the incident not discovered that causes concern," says Bill Webb, Director of Quality for Eurand in Vandalia, OH, who will discuss *Excipient Qualification Process Used by Pharma Companies — A Comparison vs. FDA Requirement* at the conference. He will describe the quality challenges suppliers face and how to be successful by working with Big Pharma. "We don't know when the next event is going to hit."

Mr. Webb and Dr. Moreton agree that such incidents occur because of rogue individuals who deliberately commit fraud, not the industry as a whole. Both concur that Big Pharma and excipient suppliers must work together to ensure the quality of excipients. ExcipientFest is helping to set standards of excellence by educating suppliers about GMP compliance and helping them interpret regulatory standards.

A BRIGHT FUTURE FOR EXCIPIENTS

There is opportunity for suppliers to be successful, says Mr. Webb. And the market for excipients substantiates that statement. Collectively, these materials accounted for a $3.5-billion global market in 2006, according to a Massachusetts-based market research firm BCC Research, which recently published the report *Excipients in Pharmaceuticals*. BCC sees the market growing at an average rate of 3.8% per year to $4.3 billion in 2011.

Growth opportunities will extend to a range of compounds and applications, according to a January 2008 report available at reportlinker.com. Based on advances in material quality and processing safety, gelatin will remain the dominant compound for drug encapsulation, warding off challenges from more expensive cellulosic and vegetable oil derivatives. Due to the breadth of existing and potential applications in drug formulations and delivery systems, cellulose derivatives will eventually evolve into the top-selling group of pharmaceutical excipients, according to the report *US Excipients Market*. These compounds will command especially strong growth opportunities as controlled-release agents and in specialty uses, such as enteric coatings and chewable tablets. Additionally, ongoing efforts to improve the bioavailability and safety of parenteral and inhalation drugs will boost demand for specialty polymer excipients, especially compounds with sustained-release and targeting properties. Multifunctional synthetic polymers, such as povidone, will broaden applications in high value-added oral medicines, including disintegrating tablets and controlled-release drug delivery systems.

Cost and quality advantages will also expand market opportunities for starch-based excipients, with pregelatinized starch fillers and binders and sodium starch glycolate disintegrants commanding the best sales growth. Based on ease of processing advantages and good compacting and compression properties, lactose will retain widespread use as a tablet filler and diluent. Sorbitol and mannitol will see the strongest demand growth among polyol excipients, according to the report, the former from uses as a liquid drug diluent; the latter from applications as a diluent in parenteral preparations. Sterile water will increase with upward trends in developing parenteral drugs, especially recombinant DNA and monoclonal antibody preparations.

Finally, efforts to reduce drug-dispensing errors and strengthen drug anti-counterfeiting safeguards will prompt drug manufacturers to use FD&C colors and specialty ink excipients.

RESPONSIBILITY LIES WITH BIG PHARMA

The increase in fraud-deterrent use of excipients reflects Big Pharma's understanding of the ultimate responsibility it has in ensuring excipient quality. "In my opinion, the ultimate responsibility lies with the product license holder; the people selling the finished product," says Dr. Moreton.

Mr. Webb agrees, "The finished product manufacturer is responsible for its drug product."


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Using excipients that deter fraud is only one way Big Pharma can take control of the situation. Drug manufacturers must play a much more active role in staying in close communication with excipient suppliers. "We can no longer use the model we used 20 years ago for dealing with suppliers," explains Mr. Webb. "Auditing suppliers every 2 to 4 years has fallen by the wayside. If a drug manufacturer suspects quality issues early on, there is a good chance the supplier can respond quickly and the problem can be resolved."

While suppliers should have an established quality system and comply with that program, Big Pharma should be focused on what makes that supplier acceptable to do business with, and have SOPs in place for making that determination. Mr. Webb says that all of this is not to say that Big Pharma has to hold the hands of its suppliers or be overly authoritative, but suppliers should recognize the opportunity they have to be successful by changing their business models to be in closer contact with pharma. "This does not have to be a contentious relationship at all, just a continuing dialogue between supplier and purchaser," adds Dr. Moreton.

Dr. Nick Buhay, Acting Director, Division of Manufacturing and Product Quality, Office of Compliance, for the FDA's Center for Drug Evaluation and Research (CDER), believes drug manufacturers should have the following elements in place to ensure excipient quality:

- Specification development based on critical quality attributes;
- Process controls that ensure consistent conformance with specifications;
- Assurance that every batch is tested to ensure conformance with all requirements for conformity with written specifications for purity, strength, and quality (Note: drug manufacturers can rely on suppliers for this testing, provided that the reliability of the suppliers' test results is validated at appropriate intervals); and
- SOPs detailing a scientifically sound approach to ensure periodic validation of suppliers' test results.

"For excipients that are critical to the quality of the finished dosage form, testing by the drug product manufacturer may be necessary to verify the critical attributes of every batch," says Dr. Buhay.

BUILDING A BETTER FENCE

Most certainly included in that dialogue will be how to comply with industry guidelines on excipient quality, and even with which guidelines to comply. The International Pharmaceutical Excipients Council (IPEC) is working to ensure the flow of safe, useful excipients to ensure safe and effective finished prescription and OTC drug dosage forms in the international marketplace. IPEC-Americas' guidelines are being harmonized with those of IPEC Europe and Japan (JPEC). This, says Dr. Moreton, is helping direct Big Pharma as it communicates with excipient suppliers.

Additionally, last year, the Bush Administration put together a task force, the Interagency Working Group on Import Safety, headed by the secretary of Health and Human Services. In November 2007, the group presented an Action Plan to the President, which contained 14 broad recommendations and 50 action steps that provide a road map for better protecting American consumers and enhancing the safety of the increasing volume of imports entering the US. Additionally, under the Plan, the FDA should have the authority to require producers of certain products to certify that their goods meet FDA standards in order to export to the US.

Mr. Webb says that part of the FDA's work will include establishing a presence in China and some of the other countries mentioned earlier. "China is a big trading partner with the US, and it does have an initiative to improve its pharmaceutical infrastructure. There are companies over there that are trying to get on this bandwagon, but they are not well trained. The FDA will work to raise awareness and the bar to weed out bad practices."

The FDA's involvement is helping to elevate the importance of excipients in formulation. "Quality characteristics of excipients are significant to the overall quality of the drug products in which they are used," states Dr. Buhay.

That significance makes it even more critical for greater control over their quality. Mr. Webb says, "Pharma and suppliers are recognizing that excipients are being elevated in importance by the FDA, and they recognize the need to be partners in order to move the industry forward and protect the safety of the consumer."

"The ultimate goal is to get the small-guy offenders that tend to fly under the radar," says Dr. Moreton. "But don't expect any one set of standards to be totally effective. A series of standards is needed to build a better fence."

THE COST OF COMPLIANCE

There is a cost to build that fence for both the auditor and the audited. If the pharma company performs the audits in-house, then an amortized cost of about $5,000 per audit in the US can be expected, says Dr. Moreton. This includes salary and payroll costs as well as travel costs. The cost of overseas audits will be higher, up to $10,000, depending on where the site is located. The costs to the manufacturer/supplier are less, heavy on time (man hours); probably costing about $2,000 to $3,000 per audit day. The costs mainly arise because the audit takes staff away from their other duties.

If third-party audits were acceptable, and the International Pharmaceutical Excipients Auditing, Inc. (IPEA) scheme or something similar could be used, then the aforementioned costs could be less, says Dr. Moreton.

"When you look at how both sides are addressing auditing, you see suppliers moving toward more group audits (multiple customers auditing at the same time), requiring payment for audits by pharma companies and having independent auditing firms perform audits and providing those reports to customers instead of agreeing to an audit by the customer," says Mr. Webb.

Reluctance on the part of a supplier to host audits is an immediate red flag, continues Mr. Webb. The supplier's reasons may be valid, but the message it sends would be of concern. "Once the concern has been created, it may result in the supplier expending additional resources to effectively address those concerns."

Audits are simply a cost of doing business in the pharmaceutical industry and tend to be accounted for in the budgeting process. We should be asking ourselves "What is the cost of not doing the audits, and not building the relationships with our customers and suppliers?" says Dr. Moreton. "What is the cost of a 483 citation from the FDA, higher insurance premiums, etc.? What is the cost of a human tragedy, such as Haiti or Panama, happening here in the US?"

"In the past, we have tended to assume that everyone is a nice guy," continues Dr. Moreton. "Well, recent events have shown us that we cannot assume anything. We have to build bridges to our suppliers and customers, amongst other things, if we are going to maintain the public trust. The public trust of pharma is shaky; we cannot afford to shoot ourselves in the foot over adulterated excipients."

About ExcipientFest® Americas: *According to Mr. Webb, ExcipientFest is setting standards for excipient quality. He says that industry must be clear that the excipient folks attending the conference are not the companies guilty of the intentional fraud discussed in this article. In its continual effort to control the quality of excipients, The Drug, Chemical & Associated Technologies Association (DCAT) has recently assumed the operation of the ExcipientFest Conference and Pharma Expo. A second event, held last year in Ireland, is also being operated by DCAT. The programs are now being presented as ExcipientFest Americas in Puerto Rico, where 9 of the world's 10 most popular drugs are produced, and ExcipientFest Europe. In addition to excipient quality, attendees to ExcipientFest Americas can attend presentations about SUPAC, Design of Experiments, Film Coating, Tablet Dosage Forms, and of course, visit with excipient manufacturers.* ◆

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By: Derek G. Hennecke, MBA

The company is for sale. You've decided that this is going to be your moment. You want a shot at it. So what's on the price tag? Unfortunately, this is not like walking down the lot at the local used car dealer. There is no "price list." Entire books have been written on how to value companies. If you're a numbers type, you have many happy hours ahead of you working through many different valuation scenarios. I'll confess, I kind of enjoyed playing with the different methodologies. But for many people, the formulas are scary. So let me give you a couple of guidelines about what others will be looking at to determine the price.

The place to start is with your company's EBITDA. That's Earnings Before Interest, Taxes, Depreciation and Amortization are taken out. You can work it out from the annual reports. Purchasers like to look at a company's EBITDA because it's a neutral way of measuring the company's cash flow. Interest, Taxes, Depreciation, and Amortization will all be different for each potential purchaser. Interest costs vary depending on the way the acquisition is financed. Taxes differ depending on location and corporate structure. Both depreciation and amortization refer to spreading an asset's cost over that asset's useful life. For example, the patent on a drug has a life of 17 years. The cost of creating that patent is spread out over the life of the patent. Amortization is used for intangible assets like patents, and depreciation is for tangible assets like equipment and buildings (unless you're Canadian and use these terms interchangeably). Depreciation and amortization depend largely on what the purchaser actually ends up paying for the company – something no one can know at this point.

A slow and steady growth company will likely use an EBITDA as an average of the last 2 to 3 years. This is a pretty solid and widely accepted starting point. A fast-growing market player might try to work with this year's projected EBITDA, though buyers are generally much more leery about accepting projections. It's safer to go with an historical EBITDA, but not as good for the seller.

Your company will sell for a multiple of your EBITDA. The tricky part is determining the multiple that applies to your company. The starting point is determining what multiple companies in your industry generally trade at. You can find a lot of information on the internet. Getting your hands on some research reports from the investment banks is even better; people listen when you quote from these guys. They listen the way you might listen to Warren Buffet drop a casual stock tip. You can find out who the important analysts are by looking at the annual All-Star Research issue of Institutional Investor; it lists top analysts sector by sector. You might try contacting your own stockbroker to see if he can help you lay your hands on a copy. He will probably have some of his own information, or may know someone who has the report you want. Keep at it. This report will be great for your credibility. I will shamelessly plug two investment bankers in our industry: Neal McCarthy of Fairmount Partners has been around the block a few times and knows his stuff. Closer to home, Gordon Ryerson from Crosstree Partners in Tampa has been very helpful.

Most companies in a mature industry go for three to six times the annual EBITDA. So if your company's EBITDA is $100,000, the purchase price would probably be somewhere between $300,000 and $600,000. Of course, there are times when large companies trade at eight or ten times EBITDA. When you buy from the stock market, you may pay 15 or 20 times EBITDA.

The difference is largely one of scale; smaller companies are simply bigger risks. They are less tried and true and more likely to have hidden problems, falsified financial statements and so forth. But there is more than just scale involved. Companies with little history and vague or questionable accounting practices will trade at the low end. Companies with solid performance histories and squeaky clean and verifiable financials will command top dollar. Then there are the hard-to-pin-down factors like future prospects, customer diversification, reputation, seller's motivation, and the number of other bidders involved. All affect the multiple.

Let's try to understand the valuation from the point of view of the money. In this case, let's assume it's a private equity backer. This guy could be your bidding rival, or he could be someone who is behind you - your new best friend. For simplicity purposes, we'll name him Bill Quickbucks. I'll talk about Mr. Quickbucks and his native habitat more in the next article, should you need to find him.

This is the guy who pretty much sets the value of most companies. Mr. Quickbucks has a small investment company and is looking for a place to put his capital that will earn him more than stock or real estate markets. Small companies are one of his best options, and that's why he likes the look of you. As a rule, Mr. Quickbucks will look for a multiple of EBITDA that will give him 30% earnings on the price of his investment (E/P). The inverse of this (P/E) is 1/0.30 and would be a multiple equal to 3.33 EBITDA. But let's assume he can actually pay a little more than that by borrowing some of the money from the bank for a tiny fraction of the interest he will collect. So Mr. Quickbucks decides to put half the money down himself and borrow the rest from a bank. By borrowing half from the bank, the price HE pays for the investment has been reduced by half, so now it is 0.5/0.30 = 6.66. That means he could pay over six times EBITDA and still be in good shape. In 2006 and the first part of 2007, things got a little bit crazy with people paying much more than that due to low interest rates, and investment companies leveraged a lot more than 50%. Your job is to figure out what purchase price would allow him to achieve his goal.

All this is based on the historical performance of the company. Obviously, you have great plans for the company, and your vision of the future most likely doesn't mirror the past. You're only going to attract Mr. Quickbucks if he's excited about this future. So how much does Mr. Quickbucks value those projections in valuing the company? Frankly, not much. Let's face it, projections are

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subjective and history is fact. Mr. Quickbucks will, quite rightly, take projections with a grain of salt. But you should still make them for your own benefit to know what your walk-away point will be. Also, Mr. Quickbucks will ask you your projections to see how confident you are of the future. If they are credible, those projections can affect that fuzzy good-feeling part of the determining of the multiple. How do you make them credible? The standard and most accepted way of projecting revenues is the book-to-bill (BTB) ratio. This ratio looks at the relationship between the sales on the books that have not yet been realized to the actual revenue the company takes to the bank each month. Take the unbilled contracts, add them up, and divide by the current month's revenue. The idea is to get a feel for how much unrealized, but solid (booked) growth the company has in its immediate future.

A rule of thumb is that a BTB of 1.30 indicates growth of 30% in the near-term. Keep in mind that near-term is relative. Stability management, for example, is booked up to 36 months ahead, while a high-throughput QC lab books month to month. The BTB is a more objective way of determining the future growth than taking a seller's word for its future prospects. But you will also want to perform some far-reaching projections. It's fairly easy to do these, and they tend to yield some pretty attractive valuations.

Start with the company's stated profits from previous years. Then adjust this number to: (1) add back non-cash expenses (i.e., depreciation), (2) add back the salaries and other compensations the owners took home, (3) add back any one-time expenses unlikely to reoccur in the future, and (4) subtract one-time revenues unlikely to reoccur.

This number represents your cash flow. Now project that cash flow into the future (say 10 years). This is where you add up all the future cash flows and reduce according to how far in the future they occur. This is called a discounted cash flow. Next year's projection may be discounted by 10%, the following year by another 10%, and so forth. Then add up all of these projections to come to a valuation.

Speaking from experience, the fact that my own projections didn't count for much was a really good thing. I'd been hired to perform a major turnaround. The company had been in the red for a few years, and I'd been working to change that. I was 13 months into the turnaround when the head office decided to sell. My projections showed the company moving into the black within 6 months and straight on skyward after that. As luck would have it, the purchase was repeatedly delayed until it fell into the month when our projections turned from red to black. I have never had a red month, and company performance has exceeded the expectations of my rosiest rose-colored glasses. But because projections didn't count for much in the valuation and the financial history of the company was dim, the important thing was that I had confidence in my projections.

You have some idea what your old stomping grounds are worth. Odds are that whatever value you arrive at is going to be more than you have in your bank account at the moment. I'll talk about where to get the capital in the next issue. Most people will start out by looking for Mr. Quickbucks, which is surprisingly easy because he's already looking for you. But there are many other options out there as well, from banks to your rich uncle, and you'll have to consider them all. ◆

BIOGRAPHY

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

BREAKTHROUGH PAIN DELIVERY

Addressing the Analgesic Gap in Breakthrough Cancer Pain – A Drug Delivery Case Study

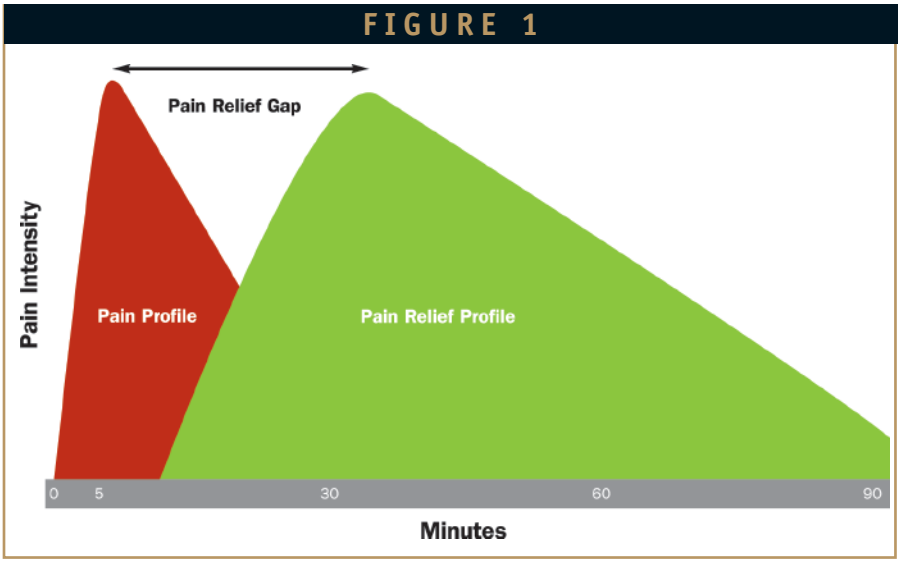
By: Josef Bossart, PhD, and Taneli Jouhikainen, MD, PhD

INTRODUCTION

Breakthrough cancer pain is a demanding challenge for patients, clinicians, and providers. Built on a background of constant pain, the breakthrough episode typically reaches peak intensity within seconds or at most a very few minutes and then resolves to background levels within an hour. It is as unpredictable in its occurrence as it is rapid in onset. While some breakthrough pain can be anticipated because it is associated with voluntary activity, in most cases, the pain arises without warning, making prophylaxis impractical.

Breakthrough pain has traditionally been treated in one of two manners. The first approach involves raising baseline pain treatment to a level where the breakthrough pain event is minimized by the higher dosage. The problem with this approach is that it means there is excess medication on board at all times, even when breakthrough events are absent. This results in an increase in the incidence and severity of side effects, such as sedation, dizziness, and constipation. The other choice for treatment is to take pain medication only when the breakthrough event arises. While this allows medication to be kept at a lower level sufficient to manage baseline pain, it requires the additional use of a breakthrough medication that can act very quickly, preferably for a period of time consistent with the duration of the pain episode. This type of pain management profile is usually associated with the use of intravenous opioids in the operating suite environment where a rapid onset of action and a shorter duration of action are desirable.

FIGURE 1



The challenge of meeting the needs of the cancer patient with breakthrough pain, while recognized for decades, received particular attention in the 1990s with clinical and epidemiological studies better characterizing the incidence and severity of the condition. At the *2001 Multinational Association of Supportive Care in Cancer* meeting in Copenhagen, Cephalon's Anthony Clarke presented the concept of the Analgesic Gap. The graphic used in his presentation to illustrate the Analgesic Gap concept is redrawn in Figure 1. The gap is very obvious; he shows the peak of pain rapidly rising to a maximum at 5 minutes and then trailing off to baseline by 30 minutes. In contrast, the peak of analgesic pain relief rises slowly to a peak at about 45 minutes and extends long after the pain event has resolved itself.

It is this gap, the difference between pain and relief that has driven the development of products to address or "fill" this gap. Filling the gap entails pushing the pain relief curve to the left so that it overlaps as completely as possible the pain curve. This article reviews some of the thinking and strategies being implemented to fill the Analgesic Gap through the rational application of drug delivery technology. It may be that we are approaching the theoretical limit for managing breakthrough cancer pain; but it has not yet reached the patient.

BREAKTHROUGH PAIN DELIVERY

HISTORICAL APPROACHES TO FILLING THE ANALGESIC GAP

The Analgesic Gap refers to that period of time in which the serum levels of an analgesic are rising but are not yet at a level sufficient to significantly treat a patient's pain. Breakthrough cancer pain on average reaches a peak within 3 minutes and then subsides to baseline within minutes or a couple of hours, with a median duration of about one-half hour. Because the pain cannot be anticipated, the use of prophylactic pain treatment is not practical. This means the patient is almost always "chasing" the breakthrough pain, because the pain intensity has rocketed off on a trajectory the patient must try and catch up with. In most cases, the patient must be content with reducing the level of pain rather than eliminating it. For the purpose of our discussion, we will use a simplified pain profile representing the median cancer breakthrough pain episode in which pain reaches a peak at about 3 minutes and returns to baseline at about 30 minutes. In many cases, the duration of the pain may be as short as a few minutes or as long as a few hours.

The earliest approach to managing breakthrough cancer pain was with the use of solid oral dosage opioids. Because the pain is severe, opioids are most appropriate. The problem with this approach is that oral opioids reach peak plasma at only an hour or so, long after the pain has passed for many patients. Even those patients with pain that lasts a couple of hours are left untreated, or poorly treated, for the first hour. One logical way to provide a better overlap between the pain curve and the opioid pain relief curve as shown in Figure 1 is to more rapidly get the opioid into the serum and shorten the time to Tmax; that is move the pain relief curve to the left. An early approach was the use of liquid formulations of opioids that are absorbed more quickly into the circulation and provide serum levels earlier than the corresponding tablet or capsule formulations. This reduces the time to maximum serum concentrations by minutes but still provides little practical improvement in pain relief for the breakthrough cancer pain patient. The cancer patient receives too little pain relief when needed but too much once the pain has subsided. In the absence of pain, opioids are only a burden.

TABLE 1

Product	Developer (US)	Presentation	T_{max}	US Status
Actiq	Cephalon	Transmucosal Lozenge	~90 minutes	Approved
Fentora	Cephalon	Transmucosal Tablet	~45 minutes	Approved
BEMA Fentanyl	BioDelivery Sciences	Transmucosal Tablet	~60 minutes	NDA Filed
Rapinyl	Endo	Sublingual Tablet	~55 minutes	Phase III
Fentanyl Spray	Insys	Buccal Spray	~85 minutes	Phase I

Transmucosal Fentanyl Products

RATIONAL DRUG DELIVERY APPROACHES – HARNESSING A BETTER OPIOID AND FASTER ABSORPTION

Anesta, now Cephalon, recognized the opportunity to improve the management of breakthrough pain by improving the delivery of an opioid and moving the pain relief curve to the left. Two strategies were pursued, a delivery system that would more quickly get an opioid into the serum and the use of an opioid that would more quickly distribute from the serum to the brain. Getting the opioid into the circulation more quickly focused on bypassing oral administration, which requires dissolution of the dose in the gut and absorption into the circulation. While intravenous administration is the gold standard for rapid delivery, it is not practical in this setting. The focus turned to transmucosal delivery, a reasonably quick route of absorption when compared with oral delivery. The second strategy looked at getting the opioid from the circulation to the brain more quickly, where it could assert an analgesic effect. The most common oral opioids, morphine, hydrocodone, and oxycodone, once in the circulation, aren't rapidly distributed to the brain. Fentanyl is much better in this respect due to its highly lipophilic nature.

By using fentanyl as the opioid and employing oral mucosal delivery, Anesta was able to provide an improvement in the onset of analgesia as compared with oral opioids. The oral mucosa, because it is rich in vasculature and relatively permeable to lipophilic products, offers more rapid absorption than the gut. Anesta's solution was Actiq, a formulation that requires the patient to rub a fentanyl lozenge on the gums for about 15 minutes. While this offers relatively more rapid and predictable uptake of an opioid and rapid distribution to the brain, it really didn't address the Analgesic Gap. With a maximum serum concentration reached only at 90 minutes, the majority of the opioid and the analgesic effects are available only long after the pain had resolved itself (Table 1).

BREAKTHROUGH PAIN DELIVERY

Building on the experience with fentanyl and trying to achieve more consistent delivery Cima, now Cephalon, developed Fentora, a fentanyl formulation no longer requiring a lozenge to be rubbed on the gums but rather involved placing a small tablet on the gums above the molars. Still requiring application for 15 minutes, Fentora no longer demanded the active involvement of the patient in dosing. Fentora provided a significant reduction in the time to maximum serum concentration from 90 minutes for Actiq to 45 minutes for Fentora. The reduction in Tmax seemingly does little to fill the Analgesic Gap experienced by the breakthrough cancer patient (Figure 2).

There are a number of additional products in development that use mucosal delivery (Table 1). These new products seem to provide a similar time to maximum serum concentration as Actiq and Fentora, but promise to offer little more to fill the Analgesic Gap.

FIGURE 2

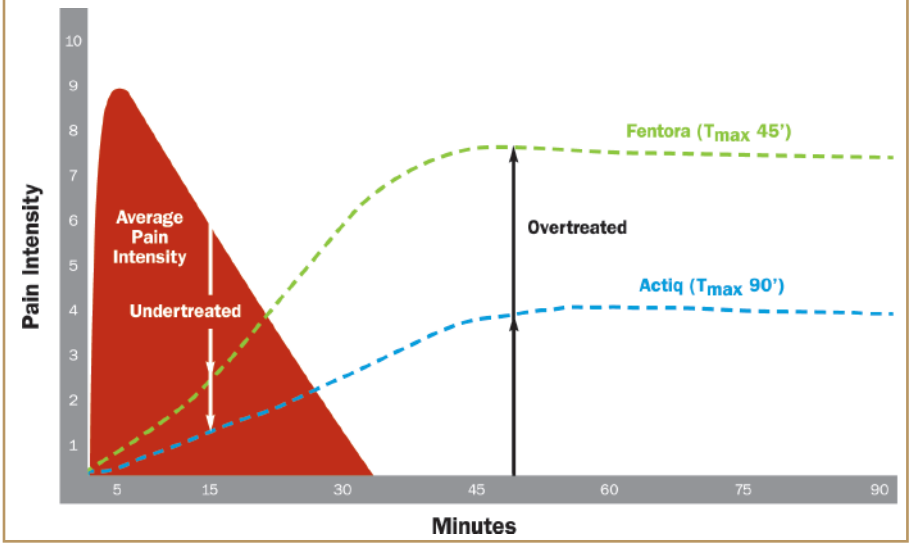


TABLE 2

Product	Developer (US)	Presentation	T_{max}	Status (US)
Instanyl	Nycomed	Intranasal	~13 minutes	Phase III
Nasalfent	Archimedes	Intranasal	~20 minutes	Phase III
Fentanyl TAIFUN	Akela	Dry Powder Inhalation	~1 minute	Pre-Phase III
AeroLEF	YM Biosciences	Nebulized	~20 minutes	Phase II
AZ-003	Endo	Aerosol Inhalation	~1 minute	Phase I

Intranasal & Pulmonary Fentanyl Products

RATIONAL DRUG DELIVERY APPROACHES – SHIFTING THE CURVE TO THE LEFT

Perhaps the greatest limitation of the transmucosal approach is the requirement that the fentanyl be absorbed over the small contact area of a tablet. The Fentora and BEMA Fentanyl (Biodelivery Sciences International) products have a mucosal contact area of only a fraction of a square inch. This restricts the absorption of fentanyl and slows the onset of action. An analogy would be an hourglass in which the drug is represented by the grains of sand. The hourglass constriction, like the small transmucosal contact area, limits the flow of sand and drug. While ideal for controlled release, this approach really is challenged to rapidly deliver enough drug to fill the Analgesic Gap.

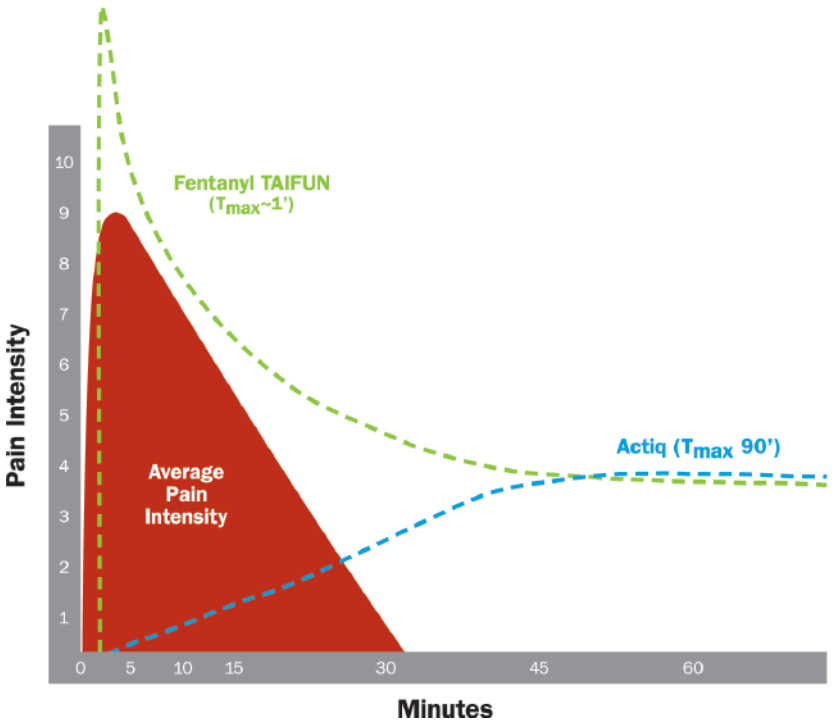
The obvious solution is to deliver fentanyl over a much larger surface area. This concept is being developed with two newer approaches (delivery to the nasal mucosa and to the lungs), both of which have a large surface area and like the oral mucosa, are rich in drug permeable vasculature. Although the lungs have a much greater surface area than the nasal mucosa, 50 m^2 versus ~1000 mm^2 (0.001 m^2), they both offer a much greater area for drug absorption than the 10- to 40-mm^2 area of an oral transmucosal formulation contact point. The resulting performance is quite significant in terms of Tmax as shown in Table 2. While peak serum levels with the oral transmucosal products are reached in 45 to 90 minutes, the intranasal and pulmonary routes provide for peak plasma concentrations within 1 to 10 minutes, approaching the theoretical limit of intravenous administration.

A direct pharmacokinetic comparison of Actiq 200 µg (Tmax ~90 minutes) and

BREAKTHROUGH PAIN DELIVERY

Fentanyl TAIFUN 200 µg (Tmax ~1 minute) a dry powder formulation of fentanyl, presented at the 2006 ASCO meeting highlights the potential for differences in onset of action (Figure 3). Overlaying these serum fentanyl plots on the breakthrough cancer pain profile, we see that the use of the pulmonary route (Fentanyl TAIFUN) offers a better match with the pain curve, with the peaks more or less overlapping. There is still an early gap in the coverage provided by Fentanyl TAIFUN and excess dosing beyond the resolution of the average pain episode, but it is potentially far superior to other approaches. It is likely that intranasal approaches will also offer an improvement over the transmucosal products, albeit not as significant as with pulmonary delivery. The intranasal fentanyl pain relief curve, with a Tmax of 13 minutes, will be situated to the right of an inhaled product, such as Fentanyl TAIFUN, but still to the left of the transmucosal products.

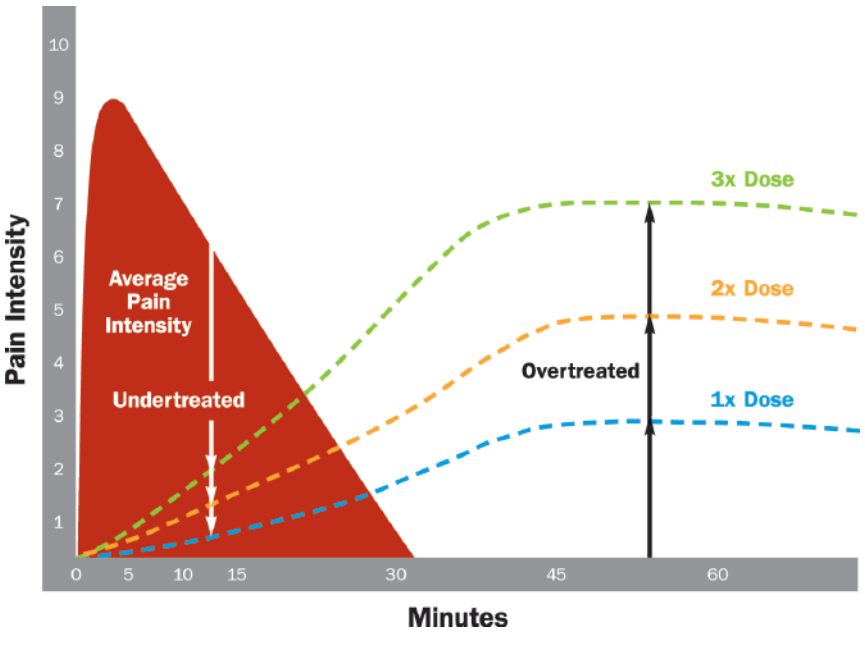
FIGURE 3



BREAKTHROUGH CANCER PAIN MANAGEMENT

There are a couple of interesting subtleties that are worth mentioning with respect to the management of breakthrough cancer pain and the gap seen with oral and oral transmucosal products. One approach that seems to be used clinically to reduce the gap with these agents is to increase the amount of drug administered. While the time to maximum serum concentrations is generally not shortened, the increased slope of the rising serum drug levels results in more drug reaching the serum sooner (Figure 4) and a partial filling of the Analgesic Gap. Although this approach can provide for more rapid pain relief, it comes with the burden of even higher serum levels of opioid once the breakthrough pain has resolved. This profile may be more

FIGURE 4



appropriate for pain that has a slower onset and lasts for several hours than it is for the rapid onset and shorter duration of breakthrough cancer pain.

BREAKTHROUGH PAIN MEDICATIONS – WHAT'S NEXT?

It seems as though we are reaching a point of optimal treatment for breakthrough cancer pain. Onset of action, as defined by new delivery systems, seems to be approaching the theoretical minimum of intravenous dosing. With respect to better opioids, there are several additional approved opioids in the fentanyl family (remifentanil, sufentanil, and alfentanil) with a similarly rapid onset of action. But without any obvious benefit in terms of onset of action or more rapid partition to the brain, it is unclear they can fill the pain gap by moving the treatment curve for the transmucosal products to the left. What they might be able to do is offer a shorter duration of action, ie, remifentanil $t_{1/2}$ 1 to 20 minutes, versus fentanyl $t_{1/2}$ 3 to 12 hours. A shorter duration of action might be useful to avoid sustained levels of opioid beyond that necessary for the breakthrough event, but not so short as to require redosing for a single breakthrough pain episode.

The concept of patient-controlled transdermal analgesia for breakthrough pain seems not to have panned out. While it would be ideal to be able to "press a button" on an opioid patch and receive a bolus of drug and pain relief, the transdermal approach has proven to be too slow in responding with adequate serum levels. Of the two products using this approach, Ionsys (active transdermal) and Titragesia (thermal enhancement), only Ionsys has received approval, not for breakthrough pain but for in-patient management of chronic pain.

The intranasal and pulmonary products are still to be approved and demonstrate their clinical benefits, although the data reported to date is very positive. Fentanyl TAIFUN as a representative of the pulmonary group has been reported to provide clinically significant pain reduction relative to baseline and placebo within about 6 minutes of administration. Published abstracts on the intranasal products report similar levels of pain relief at about 24 minutes. These times for pulmonary and intranasal delivery are consistent with their reported pharmacokinetic profiles and directly reflect on their ability to fill the Analgesic Gap.

To date, breakthrough cancer pain has been explored using almost every drug delivery approach imaginable; certainly all of the most logical ones (solid oral dosage forms, liquid oral dosage forms, transmucosal lozenges, transmucosal erodables, iontophoretic patches, sublingual sprays, nebulization, dry powder inhalation, intranasal dosage forms), hence further improvement based solely on drug delivery is hard to imagine.

In the areas of clinical and commercial opportunity, there remains significant room for improved breakthrough cancer pain formulations. It has been estimated that about 15% of Actiq is prescribed for breakthrough cancer pain, with the remainder used for non-cancer pain indications. This should not be a surprise given Actiq's poor fit with the typical breakthrough cancer pain episode. It is likely that products now in development with a faster onset of action and an analgesic profile better matching breakthrough cancer pain will be more readily adopted by cancer patients and their physicians. With some 500,000 to 800,000 Americans suffering from breakthrough cancer pain on an almost daily basis, there remains a huge gap to be filled.

BIOGRAPHY

Dr. Josef Bossart is Senior Vice President of Business Development for AKELA Pharma. Prior to joining AKELA in 2007, he held a variety of sales, marketing, general management, and business development positions during his more than 25-year tenure within the biopharmaceutical industry. Most recently, he was the founder of B4Bio, a business and corporate development services company. His earlier biopharmaceutical company experience includes vice president-level business development positions with Enzon Pharmaceuticals, GeneMedicine, and the Rhône-Poulenc Rorer group. Dr. Bossart earned his PhD in Medicinal Chemistry from the Ohio State University, College of Pharmacy. He regularly contributes industry articles in the area of drug delivery, specialty Pharma, and biotechnology.

Dr. Taneli Jouhikainen is a veteran executive with an extensive career in the medical and pharmaceutical industry. Since 1996, he has occupied development, commercial, and management positions with increasing responsibilities. Dr. Jouhikainen is currently Senior Vice President, Corporate Development for AKELA Pharma Inc. During his career, Dr. Jouhikainen has held executive positions for various companies, including President and CEO for Focus Inhalation Oy, Vice-President, Business Development & Strategy for Focus Inhalation Oy, Chairman of the Board for Spectrum Medical Sciences, and Director, Clinical Research, Leiras Oy, Research & Development. Dr. Jouhikainen is a licentiate of Medicine, Doctor of Medical Sciences, and holds an MBA. Dr. Jouhikainen has published in peer-reviewed scientific journals and is an inventor on several issued patents.

NON-INVASIVE INSULIN

Annual Update on Non-Invasive Insulin Delivery Technologies

By: Avani Amin, MPharm, PhD; Tejal Shah, MPharm; Jagruti Patel, MPharm, PhD; and Anuradha Gajjar, MPharm, PhD

ABSTRACT

The enormous progress in delivery technologies for insulin is likely to change the therapy regimen of patients suffering from insulin-dependent diabetes mellitus. The market is flooded with parenteral devices like the jects, pumps, and pens. However, the alternate routes for the delivery of insulin have also undergone a major breakthrough, and inhaled insulin, oral insulin pills and sprays, insulin patches, and nanoparticles have also hit the scene. Although the first approved inhaled insulin (Exubera) has been abandoned, other inhaled insulins are forging ahead to give it a try. Oral insulin also sees a great opportunity, and Biocon's Insugen has already been licensed for marketing in the US and China. Transdermal insulin made its presence felt with many products being developed on the basis of iontophoresis, sonophoresis, and microneedle technologies. This review presents an update on the progress of the non-invasive delivery technologies for insulin since last year's update featured in the March 2007 issue of this publication.

INTRODUCTION

Immense research and development in the insulin delivery technology market has opened new avenues that can be explored for the cure and control of insulin-dependent diabetes mellitus. Insulin accounts for a sizeable share of the overall anti-diabetic market. It is estimated that there are about 177 million diabetics globally, nearly 5% of the world population. The parenteral route for insulin has been used for decades. However, the past decade has experienced a significant change for parenteral formulations and devices. Using a syringe for injecting insulin is extremely painful for most patients and is likely to be outdated in the foreseeable future and replaced by various emerging technological innovations (eg, pen devices, jet injectors, and parenteral pumps) currently being developed. Various alternative insulin delivery methods, such as inhaled insulin (INI), oral insulin pills and sprays, transdermal patches, and nanoparticles are also ready to capture the market. The nasal route is another very promising route for the delivery of insulin.[1] This update specifically reviews the progress of the various non-invasive technologies for insulin available in the market or under clinical trials. Some newer techniques undergoing research based on the transmucosal and nanoparticles technology are also briefly mentioned.

The projected blockbuster Exubera (first approved INI), which was launched in January 2006 by Pfizer, has not been able to satisfy doctors and patients and therefore could not achieve the projected target sales. Pfizer removed Exubera from the market in October 2007. However, this does not seem to be the end of a market for the class of INI because pharma companies do have many other types and sizes of INI already in their pipeline, with a few already waiting to hit the market.

The failure of Exubera has opened avenues for the oral and transdermal insulin market. The likeliness that insulin by these alternative routes would be able to supersede the market remains to be seen. The global insulin drug market exceeded $23 million in 2004 and is currently valued at more than $5.4 billion. It is anticipated to reach $30 billion toward the end of 2014. With so many marketed formulations for non-invasive insulin, the treatment is surely to undergo a massive change in therapy regimen, which may potentially lead to a cure for diabetic patients.

INHALED INSULINS: HISTORY & FUTURE

Inhaled insulins are a novel, non-injectable alternative route for delivery of insulin in the management of diabetes mellitus. They are an important breakthrough in the history of the disease and an attractive means of treatment for many patients. Exubera, inhaled human insulin [insulin human (rDNA origin)], was a dry powder formulation and inhaler system developed by Pfizer in collaboration with Nektar Therapeutics. It was the first INI product to receive approval in early 2006 for the treatment of hyperglycemia in adults with type 1 or type 2 diabetes. It delivered short-acting human insulin powder in an aerosol form. There are a lot of studies undertaken regarding the efficacy and safety of INI. INI shows similar pharmacokinetic and glucodynamic behavior like that of subcutaneously administered rapid-acting human insulin analogues like aspart, lispro, and glulisine. It consistently improved glycemic control when used in combination with longer-acting subcutaneous insulin regimens in patients with type 1 and type 2 diabetes. It could have been used in some cases to replace or supplement oral antidiabetic therapy in

type 2 diabetic patients.[2,3]

Early clinical experience indicated that Exubera had enormous potential to be effective in treating patients with diabetes. Improved glycemic control with Exubera compared with oral antidiabetic agents, and comparable glycemic control compared with subcutaneously injected insulin had already been demonstrated.[4,5] Many previous studies have shown that Exubera was associated with greater treatment satisfaction relative to subcutaneous insulin in patients with type 1 or 2 diabetes. Most patients preferred inhaled to injected short-acting insulin, and this had some effect on quality-of-life measures.

Developing Exubera (recombinant human insulin with particle diameters between 1 and 5 microns) was a massive technical achievement, involving the stabilization of the insulin molecule to make it bioavailable in the dry powder form. It was the first insulin product that did not need to be injected, so when it was approved in January 2006, there were high expectations. Analysts estimated annual sales to be from $1 to $4 billion, and Nektar envisioned years of royalties. But the product had sales of just $12 million for the first 9 months of 2007, and it cost Pfizer $2.8 billion in pretax charges to walk away, which is rarely done when a drug has no safety or efficacy issues.[6] The possible drawbacks responsible for the failure of Exubera are summarized in Table 1.[7] Despite the approval of INI for use in adult patients with type 1 or 2 diabetes in the US and European Union in January 2006, Pfizer designed a Real World Trial to estimate the cost effectiveness of this drug and the effect of the availability of Exubera as a treatment option for glycemic control.[8] Long-term safety was found to be uncertain, and additional research was recommended into the safety, efficacy, and cost-effectiveness of inhaled insulin. At one point, the drug regarded by the company as a potential blockbuster drew severe criticism in April 2007. Despite 6 months of marketing to doctors, Exubera received only about 1 of every 500 prescriptions for insulin written in the US. Pfizer acknowledged Exubera's problems but did not give up, believing that some new marketing campaign would eventually improve the sales.[9] But Pfizer's marketing was not enough to overcome the medical, economic, practical, and legal concerns that had hurt Exubera. A recent preliminary technical appraisal from the UK National Institute for Clinical Excellence did not recommend that National Health Service doctors be permitted to prescribe Exubera for general use, stating it as "unlikely to be cost-effective."

TABLE 1

Long-Term Safety: Uncertainty of long-term safety as its use could lead to lung damage; clinical trials showed lung function to drop in some patients within the first 3 months of usage. Patients were required to take a lung function test before beginning Exubera, thus this inconvenience and testing cost discouraged doctors and patients.
Safety & Efficacy: More research required for its safety and efficacy. Exubera was a rapid-acting mealtime insulin; people who use longer-acting insulins were still required to inject as part of their routine.
Contraindications: INIs are contraindicated in smokers and in patients with bronchial asthma, bronchitis, and pulmonary emphysema.
Cost-Effectiveness: A key factor is the cost of inhaled insulin. Much more insulin has to be given via inhaler than injection; therefore, the cost of INIs is much higher than injected.
Inconvenience: Exubera is as large as a tennis ball can when it was open and had to be repeatedly pumped before the insulin could be inhaled. Thus, the inhaler was found to be bulky and hard to use.
Dose Adjustments: Exubera doses differed from those for standard insulin, and their conversions were complicated.
Alternative Options: Needles now used for conventional insulin injections are smaller and less painful than they once were. Doctors and patients had many more options for managing diabetes than they did previously.

Drawbacks responsible for the failure of Exubera[7]

After 11 years of development and barely 1 full year of sales, Pfizer dumped the much-anticipated inhaled powder insulin product. Pfizer said the decision was not the result of any safety concerns and that the drug will remain available up to January 2008 to enable adequate time for those taking it to talk with their doctors about treatment options.[10] Pfizer compensated Nektar through a one-time $135-million payment. Pfizer is also returning all rights to the product, so that Nektar can search for a new partner as it is developing a much smaller Exubera-dispensing device, which is already in Phase I trials. The new device is tentatively scheduled to be approved by 2010 or 2011, when there will be other INI on the market.

In January 2008, Novo Nordisk announced it was discontinuing its experimental AERx Insulin Diabetes Management System, which used a breath-guidance system that only delivers insulin to the lungs when breathing is correct, using strips with liquid insulin. This made dosage adjustments possible to the nearest unit. However, the AERx system (about the size of a paperback book) was the only inhaled insulin system currently in clinical trials that used a liquid formulation, requiring the insulin to be refrigerated. The company said its product was "unlikely to offer significant clinical or convenience benefits over injections of modern insulin with pen devices." Novo Nordisk was developing the inhaler with Aradigm Corp.

Does Exubera's and AERx's withdrawal mean the end for inhaled insulin? Researchers and entrepreneurs in the market do not view it as a failure for all pulmonary insulin products. Alkermes is working to develop an INI with partner Eli Lilly called AIR Insulin (currently in Phase III trials). The Alkermes/Lilly inhaler is much smaller than the one accompanying Exubera. Moreover, it's disposable, and patients receive a new one monthly. Alkermes has created powdered insulin with low-mass density but high-geometric diameter. These particles have the aerodynamic properties of small particles but the physical properties of big particles, which mean that they have low-aggregation problems, thus allowing the particles to be easily dispensable from a simple inhaler without requiring a tornado inside to atomize the powder.

Other companies are also working on the convenience aspect. MannKind has a smaller, palm-sized device to use with its powdered insulin Technosphere formulation, which has been shown to deliver higher blood-insulin concentrations than any of the other powdered products (Table 2). It's not

TABLE 2

Company/Partner	Product (Development Stage)	Formulation	Delivery Technology
Nektar/Pfizer	Exubera (marketed and withdrawn)	Dry powder	Passive inhaler the size of a flashlight, single dose only.
Aradigm/Novo Nordisk	AERx iDMS (Phase III, but as of now, program cancelled)	Liquid droplets	Small, palm-sized, all-mechanical device that does not require batteries. – Dose titrating capabilities. – Formulation requires refrigeration.
Alkermes/Eli Lilly	AIR Insulin (Phase III)	Dry powder	Disposable, small, simple, passive inhaler that fits in the palm of a hand. – Patient replaces the inhaler monthly.
MannKind	Technosphere (Phase III)	Dry power	Insulin molecules are loaded on the Technosphere particles, which are then aerosolized and inhaled into the deep lung using Mannkind's MedTone inhaler.
Generex Biotechnology	Oral-lyn (approved in India, Ecuador, United Arab Amirates)	Liquid droplets	Oral Insulin spray product (not inhaled) in metered dose through RapidMist device; absorbed through the buccal mucosa.
Kos Pharmaceuticals (now part of Abbott Labs)	Inhaled insulin (Phase II)	Dry crystals	Pressurized air delivered through hand-held breath-actuated inhaler (BAI).
BioSante Pharmaceuticals	BioAir (Preclinical)	Coated dry particles	BioAir calcium phosphate nanoparticulate delivery system.
Baxter BioPharma Solutions	PROMAXX (Phase I completed)	Dry powder	Micosphere Technology: recombinant human insulin inhalation powder is 95% insulin and does not rely on the use of inactive ingredients to facilitate delivery to the deep lung.

Current status of selected inhaled insulin products.[6,11]

yet known what effect, if any, Exubera's and AERx's failure will have on the development of these products.[6,11]

ORAL INSULIN

Ongoing research to explore new avenues for the control and cure of diabetes coupled with the recent hurdles for INIs have lead to the popularity of oral insulin formulations. Biocon's Insugen (oral insulin) is already available in the Indian market. Biocon is in the process of registering with the regulatory authorities in the developed markets for the launch of Insugen. Insugen has already been licensed to a US company for the US market and to Bayer for China.[12] Emisphere's oral insulin is in continuing clinical development (Phase II trials).[13]

There is an increasing opportunity for insulin sales by Pfizer's competitor company Generex, which launched Oral-Lyn (the company's proprietary oral insulin spray product for the treatment of diabetes) as a safe, more tolerable, and non-injectable insulin in the market. Generex entered into an exclusive product licensing and distribution agreement with Adcock Ingram Limited and Adcock Ingram Healthcare (Pty) Ltd. for the marketing, distribution, and sale of Generex Oral-lyn in South Africa and six other neighboring countries (Lesotho, Swaziland, Botswana, Namibia, Mozambique, and Zimbabwe) in October 2007. The company also received approval from the Ministry of Health of the United Arab Emirates to sell Oral-Lyn to a prominent diabetes center in the Middle East region in December 2007.[14]

Glucose RapidSpray (an spray alternative for individuals who require or desire additional glucose in their diet) is already being marketed in the US and Canada and is available in a number of leading retail chains.

The major obstacles to overcome in the oral delivery of insulin are managing to bypass the enzymatic digestion in the gut and overcoming poor enteric uptake. Scientists at Syracuse University in New York believe that conjugating insulin to B12 molecules may protect bound proteins from digestion (with B12 uptake proteins acting as a protective carrier), as well as facilitating their transport into blood serum, thus trumping the two major hurdles to oral insulin delivery.

Apollo Life Sciences' Oradel technology is based on the principle of nanoparticles compressed into tablets. Oradel nanoparticles are made up of a sugar-based protective polymer coated with vitamin B12. Insulin particles are entrapped and protected within each Oradel nanoparticle. The company is on track to become a global leader in the needle-free treatment of diabetes due to accomplishing significant milestones in development of its oral insulin tablet after successful completion of Phase I toxicology studies in February 2007. The progress of Apollo and its Oradel drug delivery technology is described in Table 3.[15]

Oramed is another leading company that has completed Phase IA clinical trials for oral insulin in the form of a capsule and has started Phase IB clinical trials. Oramed is also developing insulin suppositories for patients with type 1 diabetes, and the company expects this product will be helpful to patients for whom an oral insulin capsules are not feasible, such as small children. The product is in Phase I.[16]

INSULIN PATCHES: IONTOPHORESIS, ULTRASOUND & MICRONEEDLES

The skin being the largest organ of the human body provides a good alternative for drug delivery. Though it is a formidable barrier, it is being well exploited to transfer drugs to the bloodstream. Various transdermal delivery technologies are being developed to overcome this low-permeable barrier. The insulin patch, placed on the skin, provides a continuous low dose of insulin. Because it is difficult to overcome the skin's barriers, delivery of insulin through the skin is aided with sound waves or an electrical current or minute needles. The techniques used for the transfer of these large molecules include iontophoresis, ultrasound, or microneedles.[17]

Dermisonics' U-Strips

Dermisonics' technology is a painless, injection-free, ultrasonic transdermal drug delivery patch with broad pharmaceutical and consumer applications. The company has

integrated microelectronics and ultrasonics into a skin pad called the U-Strip. It uses alternating ultrasonic waveforms to enlarge pore diameters sufficiently for large molecules like insulin to proceed through the skin and ultimately reach the bloodstream. The system consists of four parts, including the Medi-Cap that holds the insulin, Ultrasonic Applicator, and the Dose Controller that generates ultrasonic transmissions to dilate pores and allow for the transport and controlled rate of insulin. There is also a Dose Report for physicians to download the data and enable individualized dose tracking and management. The problems of whether skin breakdown may occur and sufficient insulin can be delivered in a brief period of time to handle larger carbohydrate meals needs to be investigated.

Encapsulation Systems, Inc. announced the successful completion of its HPT-2 clinical trial comparing the U-Strip insulin patch to insulin pump therapies in type 2 diabetics. The data revealed the U-Strip will be a significant improvement over conventional pump therapy and opens the door to the market for a U-Strip patch to an underserved part of the diabetic market, namely type 2 diabetics who would be better served with actual insulin rather than traditional and often ineffective drug regimens.

Medingo's Solo

Medingo's Solo patch adheres to the skin directly and is the first truly discreet insulin dispenser that adheres to the skin underneath the clothing at any desired location on the body, without cumbersome tubing or connections. With this technology, people with diabetes can enjoy their daily activities without interruptions. Moreover, the system is designed as a discreet, lightweight, and miniature system, which is user friendly and very easy to maintain. The patch has a separate remote control unit, which is programmable and activates the delivery of insulin. It also contains an integrated blood glucose monitor as well as advanced safety features like an occlusion sensor that alerts the patient a few minutes after occlusion, warnings, alarms, and reminders. The skin break down and maximum adequate delivery issues are a cause of concern.

Vyteris' LidoSite

Vyteris' LidoSite transdermal drug delivery system uses iontophoretic technology for delivering insulin. It uses low-level electrical energy and allows precise dosing at a controlled rate that provides therapeutic and economical advantages to users. Vyteris' patented active patch technology works by applying a positive charge to the drug-holding reservoir of the patch. As most drug molecules are positively charged, the two like-charges repel, forcing the drug molecules out of the reservoir and into the skin. By controlling the intensity and duration of the positive charge applied, the smart patch controls whether the drug delivery is topical or whether the drug molecules are pushed deeper into the skin, where they enter the body's circulatory system directly. The timing of drug delivery can also be precisely controlled. The system can be preprogrammed to automatically release the drug at regular timed intervals, avoiding problems of patient compliance with multiple doses. The Vyteris active patch can also be programmed to deliver a bolus of drug on demand. In fact, drug delivery with the Vyteris active patch system can be programmed to meet the needs of the given medical situation.

TABLE 3

ACHIEVEMENTS

June 2007: Successful filing of international patent application (PCT) for Oradel.

July 2007: Issuing of positive search report by WIPO in relation to Apollo's PCT application for Oradel.

October 2007: The Syracuse research team in New York confirmed Apollo's oral insulin approach, ie, attaching insulin molecules to vitamin B12 molecules to overcome the two obstacle of oral insulin drug delivery (degradation and poor absorption).

November 2007: Pretrial tests were done and confirmed that Oradel technology protects insulin from harsh conditions in the stomach and delivers it into the intestine. These tests also demonstrated efficient incorporation of insulin molecules in protective nanoparticles as well as production of consistent-size nanoparticles.

FUTURE PLANS

To perform further nanoparticle formulation studies and move into Phase I trials in mid-2008. It includes the following:

- Optimization of the formulation of Oradel Nanoparticles further to ensure its capacity to withstand the harshest conditions of the human stomach, ie, the stomach's digestive enzymes and acids for prolonged periods.
- Studies to find the optimum time and condition required before and after a meal to administer Oradel effectively.
- Preclinical pharmacokinetic studies for assessing the safety and tolerability of Oradel insulin.

Achievements and future plans of Apollo in Oradel Technology[15]

Transpharma's Via-Derm

TransPharma is an emerging biomedical company, which has evolved the RF-MicroChannel Technology that uses a radio-frequency (RF) electrical current to create passages through the skin. This novel and unique approach provides the following advantages:

- The dimensions and density of the RF-MicroChannels enables the required dosage of the drug to be controlled very precisely.
- The drug delivery rate is determined by the size and number of RF-MicroChannels created, which enables the delivery of large and small molecules.
- RF-MicroChannels remain open in the skin up to 24 hours or more, providing high flux rates and constant drug blood-level profiles.
- The system causes minimal skin trauma and discomfort and cuts long-term side effects to an absolute minimum. The application is painless and suitable through all skin types, is fully controlled by a unique feedback mechanism not offered by any other active technology, and has maximum user comfort.

The ViaDerm Device contains an extremely accurate, disposable proprietary microelectrode array that adapts to variations both within and between skin treatment sites, and requires only minimal skin contact. The RF-MicroChannels are created by placing a closely spaced array of tiny electrodes against the skin. An alternating current at a particular radio frequency is then transferred

through each of the microelectrodes, which forms microscopic passages in the stratum corneum and outer epidermis via a process called cell ablation. The microchannels penetrate only the outermost layer of skin, where there are no blood vessels or nerve endings, minimizing skin trauma and unpleasant sensations.

Valeritas' V-Go

V-Go by Valeritas is a disposable insulin delivery device that utilizes the h-Patch technology for continuous insulin delivery. Simple-to-use, the once-daily device provides a continuous set basal rate and on-demand bolus dosing for mealtime coverage via a rapid-acting insulin analog. It helps enhance a patient's glycemic control and improve compliance. The V-Go is the smallest known FDA-cleared insulin delivery device with basal-bolus capability and no visible needle. It has received FDA 510(k) clearance, and Phase IV clinical trials are in development to support broad marketing and reimbursement claims. The h-Patch technology is also being developed to serve as a launching platform for applications across a wide spectrum of medical needs.

With clearance from the US FDA, Valeritas' h-Patch basal bolus insulin delivery system is poised to help type 2 diabetes patients improve their compliance and glycemic control with their prescribed therapy regimen. This disposable, waterproof device is small and easy to apply, making it an attractive alternative to other insulin delivery methods. It will initially be marketed to address the unmet needs of the sizeable type 2 diabetes market and with possible application to certain treatment regimens for type 1 diabetes. The h-Patch is easy, safe, and convenient. When applied, it painlessly inserts the microneedle and begins the basal flow of insulin. When a mealtime bolus is needed, the patient can press the bolus button on the h-Patch system, and a click sound indicates the delivery of the bolus. Upon removal of the h-Patch system, the microneedle retracts, locks in place, and cannot be redeployed, making the device disposal. The h-Patch system is designed to easily be replaced every 24 hours, allowing patients to rotate site placement and minimize the risk for local infection

Medipacs' Patch Technology

Medipacs is a US-based company developing a miniaturized digital pump that could become the first patch-like product to help diabetics manage their insulin therapy. The patch can be programmed with a patient's required delivery rate. The firm expects the patch to hit the $2-billion drug delivery patch market in 24 to 30 months. Medipacs' patch technology works by attaching to the skin via an adhesive and is used with skin barrier technologies, such as microneedles, phonophoresis (ultrasound), and electrophoresis (applied electric field). The pump is still in research and development, but the technology has been proven to operate over 72 hours and can sustain backpressure of 30 psi. The company hopes that larger pumps will become a commercial reality within 18 to 24 months, where it would enter an infusion pump market.[18]

There are numerous potential applications for each of these technologies, hence insulin delivery is only the beginning. Each of these companies hopes to be able to apply these methods to assist in the treatment of a variety of diseases.

ALTERNATIVE ROUTES

Transmucosal

Jain et al have reported the use of mucoadhesive multivesicular liposomes as an effective sustained-release carrier for transmucosal insulin delivery to overcome the limitations of conventional insulin therapies. The mucoadhesive multivesicular liposomes were successfully delivered through the transmucosal routes (nasal and ocular). The liposomes, coated with chitosan and carbopol, exhibited effective reduction in plasma glucose levels. The effectiveness was further demonstrated by the presence of significant quantities of ELISA detectable insulin after nasal and ocular administration.[19]

A lyophilized nasal insert insulin formulation was studied in humans by McInnes and coworkers to quantify the nasal residence time and bioavailaibility using gamma scintigraphy. The nasal insert demonstrated extended nasal residence than the conventional insulin spray.[20]

Insulin was entrapped in a new thermosensitive hydrogel prepared by simply mixing N-[(2-hydroxy-3-trimethylammonium) propyl] chitosan chloride and poly(ethylene glycol) with a small amount of alpha-beta-glycerophosphate (alpha-beta-GP) to study its potential use as nasal drug delivery system. The formulation exhibited its mucoadhesivity and the capacity to open the tight junctions between epithelial cells. The results showed that the formulation could be used as a nasal drug delivery system to improve the absorption of insulin.[21]

Nanoparticles

Nanoparticle strategies for the delivery of oral insulin have been reviewed by scientists. Polymeric biodegradable and biocompatible nanoparticles have been developed that protect insulin against degradation and facilitate the uptake of insulin. The administration of insulin-loaded nanoparticles showed improved performance in experimental diabetes and healthy animals.[22]

BioSante Pharmaceuticals has developed a formulation for delivering insulin buccally and to the lungs using its biodegradable calcium phosphate nanoparticle vehicles. This approach has potential for controlled drug release and exhibits improved bioavailability, making insulin easier to administer and less expensive. The company has completed preclinical tests showing that the biodegradable calcium phosphate nanoparticle vehicles enhance and extend the hypoglycemic effect of insulin when administered subcutaneously, buccally, and into the lungs.

A review presented by Almeida and Souto highlighted the importance of solid lipid nanoparticles for delivery of insulin through non-invasive routes. The solid lipid nanoparticles were found to be more stable and had better absorption patterns.[23]

Bhumkar and coworkers reported a novel method for the synthesis of gold nanoparticles using chitosan. They indicated better mucoadhesive properties, which lead to improved pharmacodynamic activity in rats, of the insulin-loaded gold nanoparticles.[24]

A study investigated the in vivo potential of a novel insulin-thiomer complex nanoparticulate delivery system. Insulin-loaded nanoparticles were obtained by the formation of hydrogen bonds between poly(vinyl pyrrolidone) and poly(acrylic acid)-cysteine or poly(acrylic acid), respectively. The nanoparticles administered as enteric-coated tablets or suspensions exhibited improvement in the AUC profiles and also demonstrated reduction in blood sugar levels.[25]

SUMMARY

The opening of new avenues in the research and development of the non-invasive insulin delivery market has poised to change the therapy regimen for diabetic patients. With numerous pharma companies entering the market with their unique and innovative technologies, each with its own hurdles, a

change is certain. The day does not seem to be far away when the parenteral route, which was the only suitable route, would be outdated and patients will be using alternative routes with ease and comfort. With the failures of Exubera and AERx, it may not be possible to comment on or predict how the other INIs that are ready to be launched would perform. However, the oral and the transdermal routes are gaining much importance and feature many products in the pipeline. These alternative technologies for the delivery of insulin are definitely here to stay for a long time and will be a major breakthrough in changing the lifestyles of millions of diabetics around the globe.

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BIOGRAPHIES

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Dr. Anuradha K. Gajjar earned her MPharm in Pharmaceutical Chemistry and has earned her PhD. She has more than 11 years (at under-graduate level) and more than 3 years (at post-graduate level) of teaching experience. She has been actively involved in organizing various conferences. She has published and presented papers at various national and international seminars and conferences. Her research interests include computer aided drug design, synthesis of novel heterocycles (having therapeutic potential), and analytical method development.

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ORAL DELIVERY

Oral Drug Delivery: Hurdles in Oral Product Development & the Need for Continued Technology Investment

By: Daniel Ruppar, Industry Manager, Pharmaceuticals & Biotechnology, Frost & Sullivan

INTRODUCTION

Oral drug delivery is a preferred method for many patients. For drugs targeting this route, there are typically market factors beyond efficacy that can impact marketplace penetration. As biopharmaceutical and specialty pharma products expand the importance for revenue streams for companies in the future, continued investment in oral drug delivery technologies to deliver these products to patients is expected to become increasingly important to developers.

The pharmaceutical industry is currently facing an evolutionary challenge. Issues ranging from a shift in focus areas for growth investment, IP issues, generic expansion, and continued increased safety scrutiny of products are forcing companies to transition their strategies in order to remain relevant in a changing market. The need to understand and align with areas of growth opportunity, such as biopharma and specialty pharma, and to evaluate new forms of life-cycle, portfolio, and pipeline management strategies are all of paramount importance. Furthermore, as companies look to improve their margins, the necessity to look outside their own organization through outsourced research, manufacturing, and partnership development with drug delivery companies is expected to play an important role in future product development.

When developers are assessing drug development opportunities, a recurring issue is the drug delivery method. Even past the route of delivery, the technology behind the process can be an important factor, especially when products are being formulated using release technologies. Beyond this lies patient considerations in terms of what attributes either they or their prescribers could consider important. Here, issues such as side effects, dosing frequency, and convenience, can be important in terms of driving prescriptions to or from products in the marketplace. These factors also can often differentiate products from competitors, and can be key points in terms of providing a competitive advantage.

Unfortunately, oral drug delivery falls short when it comes to the delivery of large molecule drugs. Currently, companies are continuing to drive the inclusion of biotech drugs in their product portfolios. The recent effort of Novartis through their announced collaboration with MorphoSys for biologics shows that companies are attempting to maintain relevancy by integrating and expanding centers of new growth potential. This is a continuous concern in an industry recently faced with widespread cost cutting and lay-offs in various areas in an effort to improve factors, such as margins and corporate performance. The efforts of companies to develop technologies that can deliver biopharmaceuticals orally are expected to continue to be explored and needed by developers as they seek to meld patient preferences with the new product opportunities in biopharma.

PATIENT HURDLES

Oral drug delivery is typically seen as the preferred route of administration for drugs. This, however, is not consistent across all regions or in all therapy settings. For example, in Japan, delivery via a transdermal patch is held in high regard by patients. In the US, the preference still routes to oral. When Frost & Sullivan surveyed US patients about their perception of oral drug delivery versus other methods (eg, injectable, intravenous, transdermal patch, etc), they associated oral delivery with characteristics, such as ease of self-administration as well as convenience and low cost. However, not all patient perceptions for oral delivery are totally positive, as some consider the route to be slow acting compared to other types.

Even if bioavailability is achieved in a clinical setting, that realistically is often not enough for the oral drug to see an effective conclusion of the trials process or robust performance in the marketplace. Other hurdles in terms of patient factors often emerge. For example, in an oral heparin trial, patients were given Rolo candies post drug dose in order to mask the bad taste of the investigational drug product. Realistically, that's something that would need to be rectified if that version of oral heparin would have any hope of being marketed, or have patients actually want to use it. In addition, with oral heparin, because it is unfractionated heparin, there are other issues, such as monitoring needs to watch for things like HIT (heparin induced thrombocytopenia) and an issue of dose frequency.

For marketed oral drugs, frequency of dosing is a big concern. This is one reason why companies develop oral extended-release forms of marketed products, which could improve that attribute. Extended-release technologies can also improve side-effect profiles and offer life-cycle management opportunities. Outside of release technologies, other improvements in terms of oral delivery are also sought by companies. However, even if dosing improvements are made, often the total package of patient experience is not enough for the product to see widespread uptake or blockbuster sales potential. In the case of the cholesterol drug Welchol, a variety of improvements were made over the competing bile acid sequestrants. The elimination of the need for the patient to take large amounts of powder, and the GI side-effects benefits that were obtained through the engineering process for Welchol position it with a competitive advantage to the other drugs in its class.

However, when faced with cholesterol drugs in other classes, the product does not fare as well and gets hit with the frequency-of-dosing problem, among other issues.

In cholesterol therapy, a trend is in the use of combinations of products in order to maximize the reduction of LDL-C (low density lipoprotein cholesterol). Most patients use statins or a combination of a statin and non-statin product, of which there are few options. Compared to a non-statin like Zetia (Merck Schering-Plough, Cholesterol Absorption Inhibitor), when patients are looking to add another drug, or only use a non-statin, Welchol isn't typically first choice due to the much higher frequency of dosing, large pill size, and GI side effects. Here, with Zetia and Welchol having similar efficacies (~18% reduction in LDL-C), if a patient is faced with six pills a day with Welchol and a once-daily with Zetia, Zetia is probably going to win out due to the lower frequency of dosing, even without getting to the side-effect consideration. Therefore, even though Welchol improved the oral delivery of a bile acid sequestrant, the total package isn't enough to propel it to widespread prescribing or the blockbuster level like Zetia. Welchol is expected to remain more of a niche use product falling in the $100- to $200-million range (US) as it does meet the need for a non-systemic option, or a drug for non-responders to other classes who require drug therapy to lower LDL-C. In terms of revenues for non-statin brands, however, Welchol is the lowest of all marketed drugs.

FINDING AREAS OF OPPORTUNITY

Opportunity for new product development with an oral drug is not limited to scenarios, such as the creation of an oral form of a syringe delivered product or by using a release modification technology. In areas where a brand opportunity arises for new products, new branded oral drugs could have a significant revenue potential, especially if product characteristics can improve upon those drugs in the market. In the area of oral anticoagulants, such an opportunity exists. In the US, the only product marketed is warfarin (Coumadin), which has been in use for decades and is off-patent. Developers have been working to take advantage of this opportunity for some time. AstraZeneca's Exanta, an oral direct thrombin inhibitor (DTI), a much touted potential successor in this space, was approved in Europe but was denied in the US by the FDA and later pulled from the market entirely. Other high-profile pipeline efforts from Boehringer-Ingelheim (Rendix – oral DTI) and Bayer (Rivaroxaban – Factor Xa Inhibitor) continue along the development pathway, as well as a list of compounds from other developers of all sizes.

Here lies an issue that plagues many oral compounds due to the systemic nature of the delivery. Even if efficacy is achieved, compounds, even in the latest stages of the development process, can be torpedoed by liver toxicity issues (Exanta) or other flaggable problems. This serves to underline the increasing importance the FDA is placing on product safety. Also, when spotlight issues emerge, trial designs should serve to capture data that can prove to differentiate compounds from failed ones in terms of the overall safety profile. In the anticoagulant area, compounds of both leading pathways (Factor Xa, DTI) can expect to be under scrutiny in terms of their overall safety profile. Warfarin itself is far from an ideal drug. However, the FDA is not going to allow a new drug to hit the market that could supplant warfarin if there are other potential safety issues. Therefore, until someone can successfully demonstrate differentiation through efficacy and safety profiles that can show benefit to patients on both sides of the issue, billions in revenue potential sits untapped for a new oral anticoagulant.

FUTURE ORAL DEVELOPMENT

With the need to incorporate oral drugs based on a variety of technology platforms, the continued design of drug delivery technologies applicable to biopharmaceutical as well as small molecule drugs is expected to continue. Especially with patient preference remaining orally focused on the whole, continued efforts in developing drugs to be delivered via this route, especially for out-patient, chronic disease medications should remain. With increasing future needs for companies to derive products out of specialty pharma, an area not dominated by oral delivery, continued investment in oral drug delivery technology platforms that can meet the needs of those products would serve the industry well.

BIOGRAPHY

Mr. Daniel Ruppar is the Industry Manager of Frost & Sullivan's North American Pharmaceutical & Biotechnology analyst team. He focuses on monitoring and analyzing emerging trends, technologies, and market dynamics in the pharmaceutical and biotechnology industry in North America. Since joining Frost & Sullivan, Mr. Ruppar has worked in the areas of cholesterol therapy, thrombosis, diabetes, colorectal cancer, drug delivery, and specialty pharmaceuticals. He also has performed consulting duties for the venture capital industry. Prior to this, Mr. Ruppar spent 9 years in the pharmaceutical industry as a medicinal chemist. Additionally, he is a co-author of multiple scientific publications in peer-reviewed journals for his work in chemistry, has authored multiple articles in Drug Delivery Technology, and is a co-inventor on four patents for his work in drug discovery. He earned his BS in Biochemistry with a minor in Economics from Trinity University.

LIFE CYCLE MANAGEMENT

Life Cycle Management: Taking an Aggressive Approach

By: Douglas Martin, MD

INTRODUCTION

What should you do when your blockbuster is being legally copied and sold for a fraction of the cost? For pharmaceutical companies, the answer should be to create a sequel with nearly the same cast, and then target a new audience. In taking an aggressive "strategic innovation" approach, companies should leverage years of research to identify molecular entities similar to an expiring blockbuster, and erect new exclusivity barriers for these follow-on drugs by targeting strategically chosen indications. This approach relies on purposeful coordination across functional teams to mitigate clinical development risk and to ensure a favorable reimbursement environment that will allow the follow-on to generate blockbuster-like returns.

THE NEED FOR A PROACTIVE LCM APPROACH

Traditional product life cycle management (LCM) strategies are defensive plays that aim to preserve market share in the face of lower priced generics. For example, reformulations of popular drugs, often launched late in a product's life cycle, try to compete by increasing dosing convenience. While this is a popular strategy, with reformulations making up over 50% of all new NDAs between 2002 and 2005, only a few companies have succeeded in extracting any real value out of these programs.[1] The high-failure rates are attributed to an inability to garner higher reimbursement for increased dosing convenience. For example, Lilly's Prozac Weekly, the 2001 follow-on to the 1990s blockbuster Prozac, did not enjoy preferred payor tiering, and as such, US revenues collapsed from $2.05 billion in 2000 to $30 million in 2006. Importantly, even successful LCM strategies that focus on pediatric extensions and new indication identifications only extend exclusivity barriers for 6 months and 3 years, respectively.

THREE KEY INITIATIVES FOR A STRATEGIC INNOVATION PROGRAM

Strategic innovation approaches combine marketplace knowledge and internal R&D resources to protect against generic competition for far longer than traditional approaches. Successful application of strategic innovation can extend exclusivity for nearly 14 years compared with approximately 3 years with traditional approaches. In order to execute strategic innovation, companies should form three initiatives.

Initiative 1: Closely Monitor Off-Label Use & Small Investigator-led Studies

Companies must continuously monitor real-world prescription patterns and keep track of small evidence-based studies supporting novel uses. It is estimated that nearly 20% of outpatient prescriptions are written for clinical indications for which the drug has not been FDA approved.[2] Understanding the true market for products may point to a new direction years before patent expiration. Furthermore, initiating clinical studies in the new condition is likely to involve less risk given the early "open-label" signal showing a potential benefit in human subjects.

In a nearly flawless example of strategic innovation, Pfizer leveraged its in-house knowledge of GABAergic pathways to create Lyrica (pregabaline) as a follow-on to Neurontin (gabapentin). As early as a year after launch of Neurontin, small investigator-led clinical studies suggested that GABA agonists, and Neurontin in particular, have a clinical benefit in chronic pain states. Additionally, monitoring off-label prescriptions of Neurontin (estimated to be up to 86% of all Neurontin prescriptions) revealed extensive use in a variety of pain indications with anecdotal clinical pain relief. Using

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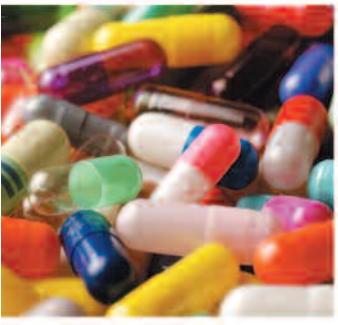

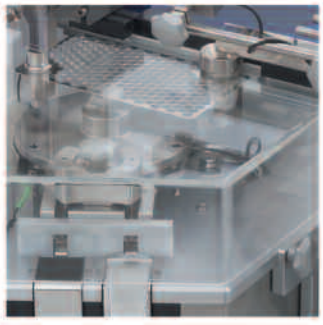

Utilize capsules.

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

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

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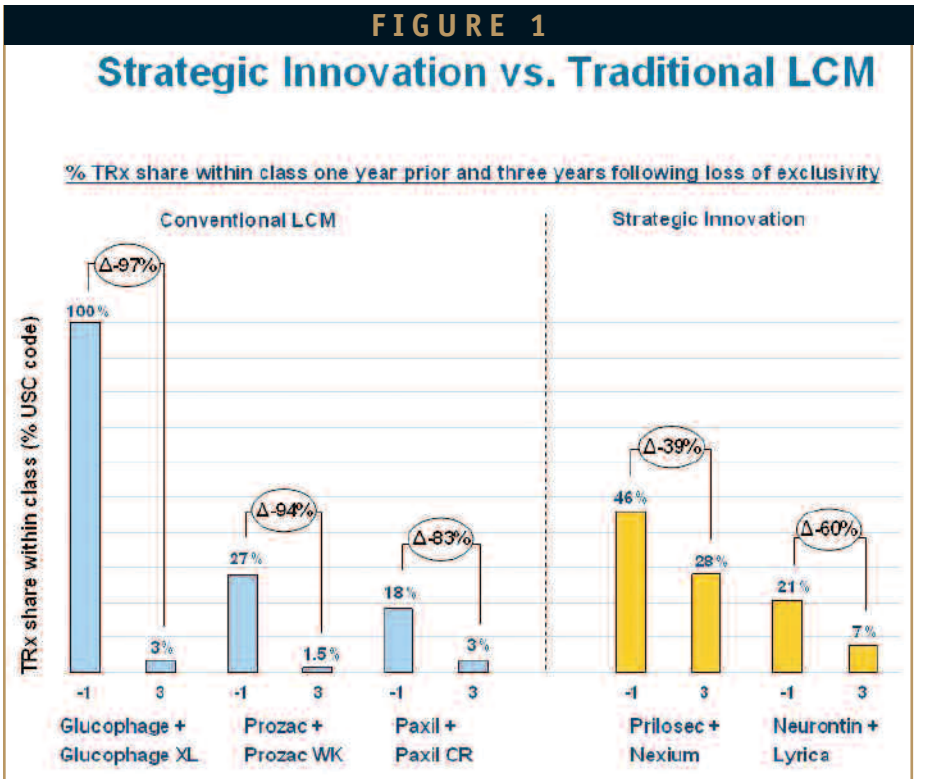
this data, Pfizer designed Lyrica's clinical trials to test for epilepsy, the original indication of Neurontin, as well as neuropathic pain. The bet paid off when Pfizer received FDA approval for use of Lyrica in peripheral neuropathic pain in diabetic patients in 2004.

By leveraging use of a predecessor drug combined with a strategically chosen Phase III trial, Pfizer differentiated Lyrica as the go-to therapy for the new pain indication. The company exploited the move to "evidence-based medicine" for its new indication and insulated itself from payor pressures to use soon-to-market gabapentin generics because Neurontin was never indicated for pain. Generic manufacturers of gabapentins are unable to prove efficacy equivalence in the absence of bankrolling their own trials, and are unlikely to do so. Moreover, Lyrica enjoys both FDA-granted NME exclusivity and new compound and medical-use patents, thus allowing Pfizer to recapture long-term revenue streams from essentially the same drug. Lyrica is now projected to reach blockbuster status by 2007 with sales of $1.1B.

Initiative 2: Identify a Franchise of Similar Compounds to Target Related Conditions

Accumulated R&D knowledge of chemistries and biological pathways must be leveraged to create a family of similar drugs. Traditional reformulations involve using the same active moiety and extending exclusivity for merely 3 years. However, R&D teams should develop similar, yet "enhanced," drugs from the appropriate drug class to exploit both FDA exclusivity and new patents. This approach allows extending franchise revenue streams for the maximum term (eg, 20 years, including development time).

FIGURE 1



Franchise-based market share year -1, +3 for selected blockbusters (IMS and DataMonitor 2005).

For example, AstraZeneca's once-daily Nexium is a single-isomer version of the predecessor Prilosec. Compared to Prilosec, Nexium has decreased hepatic metabolism and slower plasma clearance, thus resulting in improved plasma concentration and better acid suppression. However, improved kinetics alone would have led to a "me-too" proton pump inhibitor (PPI) that would have fallen to generic competition and payor restrictions as did TAP Pharmaceutical's blockbuster Prevacid. On the other hand, AstraZeneca differentiated Nexium in a crowded PPI class by performing clinical trials showing a faster response benefit in GERD in addition to healing of esophageal ulcers.[3] Furthermore, AstraZeneca performed trials showing that Nexium also helps reduce the risk of NSAID-associated gastric ulcers, a benefit established in previous smaller clinical trials. The combination of a similar, but new molecular entity, and a suite of strategically chosen indications allowed AstraZeneca to distinguish Nexium from what was considered a class effect. As a result, AstraZeneca placed Nexium as the first-line choice among mostly similar compounds. Pricing Nexium favorably to Prilosec has allowed the compound to capture $5.1 billion of the $14-billion 2006 US PPI market that includes inexpensive generics.

Initiative 3: Maintain Tight Communication Between Commercial & R&D Teams

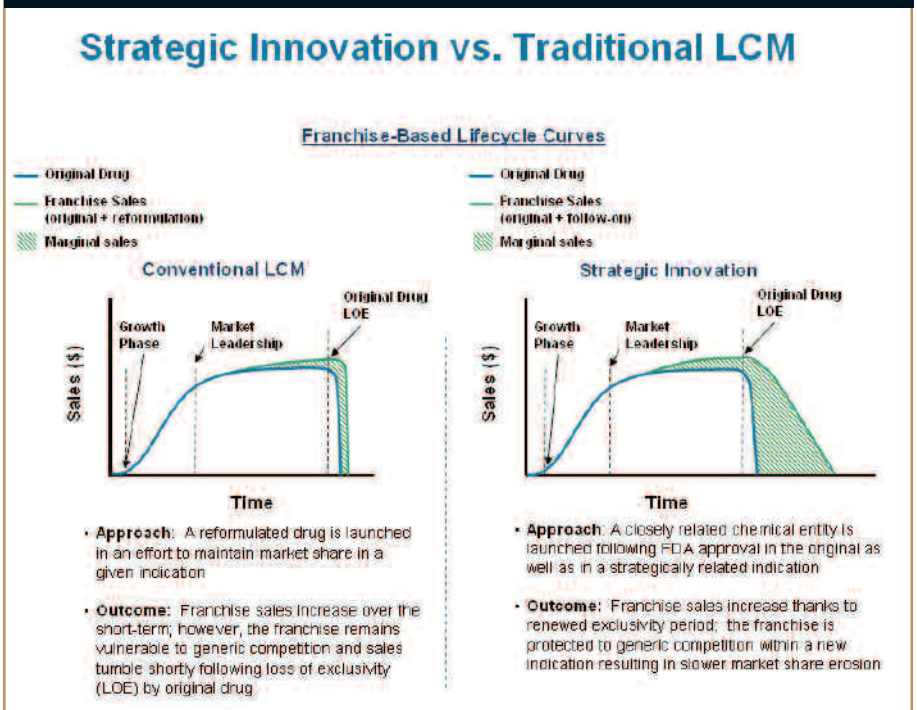
A cross-functional team composed of R&D and brand and marketing teams should accompany a successful compound throughout its life cycle and continuously evaluate both therapeutic and economic potential of emerging molecules and indications. An early combined team approach significantly mitigates development risks associated with the launch of the next-generation product. The R&D team's significant know-how about drug classes

accumulated over time should translate into a suite of related compounds with known efficacy and safety data. The commercial team's responsibility should be to identify lucrative markets and create effective communications that can be used to strategically position promising new drugs for novel yet related indications. The teams must be managed to effectively share information and make joint decisions as to the best direction a particular franchise should expand.

SUMMARY

Strategic innovation is meant to augment traditional LCM approaches. Evidence of multiple blockbuster follow-on drugs, such as Lyrica and Nexium, suggest that pharmaceutical companies can successfully perform strategic innovation. While the development costs of reformulations are significantly lower than strategically innovated products, the rewards are significantly lower as well. Average development costs of reformulations run $80 to $100 million compared to $700 million for strategically innovated products. However, returns for reformulations are usually far below that of the predecessor drug and narrowed to approximately 3 years given limited exclusivity (MEDACorp Analysis, DataMonitor). Strategic innovation drugs may achieve blockbuster status themselves with an exclusivity period comparable to a new patent life. Strategic innovation allows companies to go on the offensive, leverage years of research for longer, and develop a franchise of follow-on drugs that generate revenue streams long after the initial blockbuster is retired.

FIGURE 2



Theoretical graphic (2 x 2) of revenues over time for traditional strategies versus strategic innovation (MEDACorp Analysis).

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BIOGRAPHY

Dr. Douglas Martin joined Leerink Swann Strategic Advisors after his work at McKinsey & Company, where he primarily focused on building new business and corporate-wide strategic issues for his Fortune 500 and new-economy healthcare clients. He completed his residency work in Internal Medicine at Brigham & Women's Hospital and served as a teaching fellow at Harvard Medical School. Dr. Martin is a graduate of the University of Pennsylvania School of Medicine, where he was elected to the Alpha Omega Alpha Medical Honor Society. He completed his undergraduate degree with Great Distinction at McGill University in Montreal, where he was named University Scholar.

SOLUBILITY CALCULATOR

Measuring the Solubility of a Model Drug in Drug-in-Adhesive Transdermal Patches to Validate a Theoretical Solubility Calculator

By: Rachael Myatt, Gbolahan Oladiran (PhD student), and Hannah Batchelor, PhD

INTRODUCTION

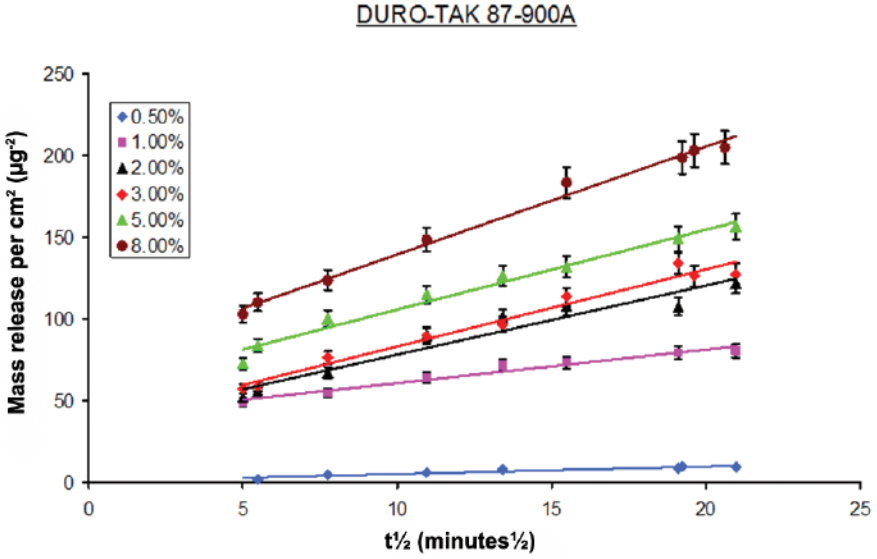
Transdermal drug delivery is an important and continually expanding field of research and development. The development of transdermal drug delivery systems (TDDS) requires a choice of polymer with optimum drug solubility. A saturated system should provide the highest thermodynamic potential and therefore the maximum rate of drug penetration.[1] Measurement of drug solubility within these TDDS is important as it can be used to predict the in vivo performance of a product.[2]

Measurement of drug solubility in semi-solids is difficult and time consuming; however, an online solubility calculator based on linear free-energy relationships is available at www.transdermaladhesives.com for the DURO-TAK® range of acrylic adhesives often used in the formulation of TDDS. The drug's Log_{10} of the octanol-water partition coefficient and its solubility in water are the required inputs for the solubility calculator. This was previously only validated via microscopy, used to observe the drug loading at which solid material was first visible, and provided only semi-quantitative data.[3] The following research aimed to validate the use of the theoretical solubility calculator by comparing the solubility of sodium fluorescein, a model hydrophilic drug, in a range of DURO-TAK adhesives using Higuchi kinetics to measure the experimental solubility.

METHOD

Drug-in-adhesive patches were prepared at six different sodium fluorescein-loading

FIGURE 1



Graph showing the results for the mass of sodium fluorescein released per cm² (µg.cm⁻²) against the square root of time for adhesive DURO-TAK 87-900A.

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concentrations using DURO-TAK 87-900A, 87-9301, (3)87-2525, and 87-2852 adhesives. At least three concentrations on either side of the theoretical solubility (as predicted using the online tool) were prepared. The release of drug from each formulation was measured using a dissolution apparatus over an 8-hour period. Phosphate-buffered saline at pH 7.4 (PBS) was used as the dissolution medium. A 1-ml sample was taken at the specified time point and replaced with fresh PBS to ensure sink conditions. The samples were then analyzed using a Spectra Max Gemini XS micro-plate reader at an excitation wavelength of 490 nm and an emission wavelength of 515 nm. The concentration of fluorescein released was determined according to a previously constructed calibration curve (linear regression $r^2 > 0.99$). The release profiles were fitted to Higuchi kinetics, and a plot of the release rate constant versus drug loading for each adhesive was plotted, where the inflection predicted the solubility.

RESULTS & DISCUSSION

The data collected for each adhesive was fitted to Higuchi kinetics as shown in the graph below for adhesive DURO-TAK 87-900A, to allow the release rate constant, K_H, to be calculated as the gradient of the line according to Higuchi.[1]

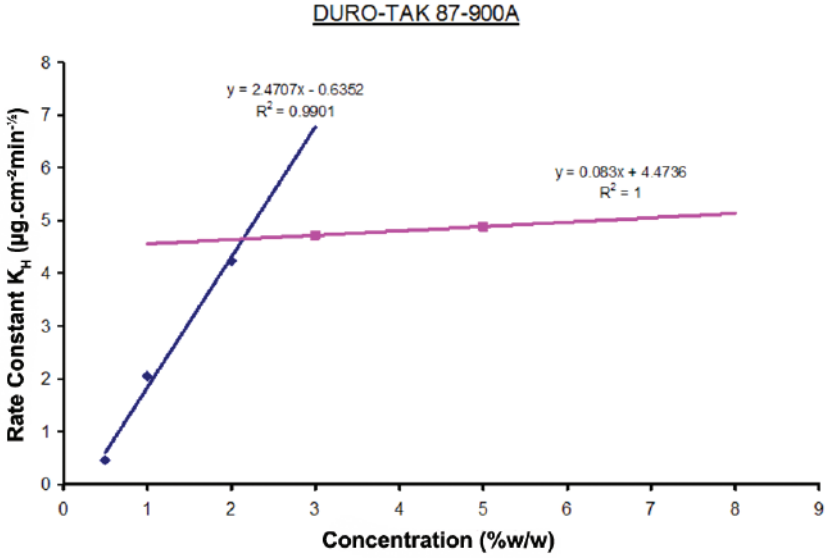
Higuchi stated that the release rate constant is dependant upon the nature of the drug present in the vehicle, with soluble drug providing a different relationship compared

TABLE 1

DURO-TAK® Adhesive	Predicted Solubility (%w/w)	Experimental Solubility (%w/w)	Difference (%)
87-900A	2.579	2.337	-9.38
87-9301	3.161	3.507	+10.95
(3)87-2525	2.001	2.557	+27.79
87-2852	1.686	1.465	-13.11

Comparing the predicted and experimental solubility found for sodium fluorescein in a range of DURO-TAK® adhesives.

FIGURE 2



Graph showing K_H against concentration for adhesive DURO-TAK 87-900A, the inflection of which gives the solubility of sodium fluorescein, in this case, 2.337 %w/w.

to suspended drug. Therefore an inflection in a plot of K_H against drug loading (%wt) provides an experimental solubility value of sodium fluorescein in the adhesive.[1] These plots were also created for all drug systems investigated to predict the experimental solubility, and the results are listed in Table 1.

The experimental values determined were in close agreement with the predicted values given by the solubility calculator. DURO-TAK adhesive (3)87-2525 gave the largest difference, although during formulation, it was noted that the fluorescein did not blend with this adhesive to the same extent as with other adhesives, which may explain this somewhat larger discrepancy.

CONCLUSION

It can be said that the solubility calculator provides a good estimation of solubility as validated using Higuchi analysis. A previous study performed by Foreman et al showed differences of up to 100 % between experimental and theoretical solubility values in which microscopy was used to validate this model.[3] The study has confirmed that the solubility calculator would be of some use to TDDS manufacturers to find the optimal DURO-TAK adhesive to use, therefore reducing the time span of previously heavily time-consuming preformulation studies.

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3. Foreman P, Luciano A, Yang H, Jacobson S. Predicting drug solubility in transdermal adhesives. Drug Delivery Tech. 2005;5(7):46-51.

BIOGRAPHIES

Ms. Rachael Myatt has just completed her undergraduate studies in Pharmacy at Aston University, Birmingham, UK. She is now undertaking her pre-registration year within community pharmacy.

Mr. Gbolahan Oladiran is a post-graduate research student (PhD) within the School of Life and Health Sciences, Aston University, UK. His research is focused on development of novel delivery systems for transdermal applications.

Dr. Hannah Batchelor is a lecturer in Pharmaceutics at Aston University, UK. Her area of expertise focuses on bioadhesive drug delivery devices; such systems are of interest as they offer the potential to increase the absorption of drugs by both specifically adhering to absorptive membranes and minimizing diffusion barriers. In particular, she has investigated systems to target the upper GI tract for oesophageal reflux disease, oropharyngeal infection, and oesophageal motility disorders. Recently, she has researched adhesive transdermal formulations for improved efficacy with particular emphasis on determination of the solubility of drugs within transdermal formulations. She has published work comparing the use of HyperDSC, release kinetics, and microscopy as tools to determine the solubility of drugs within semi-solids.

DRUG DELIVERY Executive

SCOLR Pharma, Inc.
Self Correcting Oral Delivery Systems

SCOLR Pharma, Inc.: A Differentiated Oral Drug Delivery Company

Based in Bellevue, WA, SCOLR™ Pharma is engaged in the development and licensing of its Controlled Delivery Technology (CDT®) to address challenging formulation needs and to create novel pharmaceutical products. The CDT platform consists of several patented oral drug delivery technologies for over-the-counter (OTC), prescription, and nutritional compounds. Currently, SCOLR is applying its expertise to a pipeline of potential products in various stages of development. Drug Delivery Technology recently interviewed Mr. Daniel O. Wilds, President and Chief Executive Officer of SCOLR, to discuss how the company intends to commercialize these products independently and through third-party alliances with pharmaceutical and other industry partners. The company's stock is traded on the American Stock Exchange (AMEX) under the symbol DDD.

Mr. Daniel O. Wilds
President & CEO
SCOLR Pharma, Inc.

"Our innovative and patented CDT-based drug delivery technologies enable us to rapidly formulate tablets or capsules that release their active agents predictably and programmably over a specified timeframe of up to 24 hours. Our platform is designed to reduce the frequency of drug administration, improve the effectiveness of the drug treatment, ensure greater patient compliance with a treatment program, reduce side effects, and increase drug safety."

Q: Can you tell us a little about the history of SCOLR Pharma, Inc.?

A: The name SCOLR is an anagram for self-correcting oral linear release, just one of the important capabilities of our CDT oral drug delivery platform. The initial constituents of our platform were licensed from Temple University in 1998 while we were developing, manufacturing, and selling shelf-stable probiotics and animal health products. After evaluating our initial prototype CDT formulations and following the issuance of two licensed CDT patents, we completed the divestiture of our non-CDT-related businesses by December 2003 to focus exclusively on building a specialty pharmaceutical company based on our expanding CDT drug delivery platform.

Today, our CDT technology is composed of five issued patents and numerous patent applications. These form the basis of our growing portfolio of commercialized extended-release nutritional products and our differentiated pipeline of potential OTC, prescription, and consumer products. Currently, more than 200 million CDT-based nutritional tablets have been produced by our partners and distributed via large private label retailers. We have completed 18 validating human clinical trials for multiple pipeline-related product applications.

Q: What are some of the benefits of SCOLR's drug delivery platform, Controlled Delivery Technology (CDT)?

A: Our CDT suite of patented technologies enables a new generation of less complex, cost-effective controlled-release tablets and capsules and is applicable to a broad range of drug types, classes, and consumer products. Our technologies provide novel formulations with robust, predictable, and programmable drug release using generally regarded as safe (GRAS) ingredients. Typically, our CDT formulations are produced in a simple two- or three-step manufacturing process using standard granulation, blending, and tableting or encapsulation equipment.

In addition to extended-release applications, our platform can provide improved oral bioavailability and consistency without the use of costly or complex nano-crystalization, micro-milling, or coated particle technologies. CDT also allows for gastro-intestinal (GI) stability and can achieve a broad range of release profiles often in a simple, eloquent monolithic tablet formulation.

Q: Can you briefly discuss your current licensing and development agreements?

A: We have developed multiple private label extended-release nutritional products incorporating our CDT platform that are sold by national retailers. In October 2005, we entered into a strategic alliance with a subsidiary of Perrigo Company for the manufacture, marketing, distribution, sale, and use of certain dietary supplement products in the United States. We receive royalty payments based on a percentage of Perrigo's net profits derived from the sales of products covered by our agreement.

We have a research collaboration with BioCryst Pharmaceuticals to develop an oral formulation of peramivir, a promising antiviral compound, using our CDT platform. Peramivir is a novel therapeutic being developed by BioCryst for treatment of seasonal and life-threatening influenza with a focus on intravenous and intramuscular delivery. The goal of the collaboration is to develop an oral delivery system for peramivir that improves bioavailability.

We have also entered into a collaboration and license agreement with Dr. Reddy's Laboratories to pursue development and commercialization of an undisclosed oral prescription drug with significant potential for the cardiopulmonary market using our CDT technology.

In addition, we are developing other products that we have not disclosed for competitive reasons, and we are evaluating additional drugs as potential development candidates for expanding our growing portfolio of CDT applications.

Q: What makes SCOLR attractive as a formulation business partner?

A: Our innovative and patented CDT-based drug delivery technologies enable us to rapidly formulate tablets or capsules that release their active agents predictably and programmably

over a specified timeframe of up to 24 hours. Our platform is designed to reduce the frequency of drug administration, improve the effectiveness of the drug treatment, ensure greater patient compliance with a treatment program, reduce side effects, and increase drug safety. And as stated earlier, our technology can be incorporated into oral formulations to increase the oral bioavailability of previously non-soluble and sparingly soluble drugs without employing costly or complex nano-crystalization, micro-milling or coated particle technologies. We believe CDT offers significant advantages over traditional drug delivery systems and therefore makes SCOLR an attractive partner.

Q: What is SCOLR's strategy for growth going forward?

A: We intend to continue to utilize our broadly applicable CDT drug delivery platform to build a major specialty pharmaceutical company based on our growing portfolio of differentiated and patent-protected internal and partnered OTC, prescription, and nutritional products. Consistent with our strategy, we continue to advance our lead product candidate, an OTC 12-hour, extended-release CDT-based formulation of ibuprofen. We are completing our pivotal trials with the intent to submit our first New Drug Application in 2008. Ibuprofen is an analgesic typically used for the treatment of pain, fever, and inflammation, and there are currently no extended-release formulations of ibuprofen approved for use in North America.

In addition, we have completed clinical trials for our OTC 12-hour, extended-release pseudoephedrine formulation that is one-third the size of the currently marketed reference product with an equivalent drug load. We are preparing supporting documentation for CDT-based pseudoephedrine for submission of our first Abbreviated New Drug Application in 2008. Pseudoephedrine is a decongestant that is widely used to relieve sinus pressure related to allergies and the common cold.

We are also engaged in developing CDT-based extended-release formulations of ondansetron, rivastigmine, and risperidone, as well as an immediate-release formulation of raloxifene. Ondansetron is the active ingredient drug in Zofran®, GlaxoSmithKline's product for anti-nausea and vomiting associated with chemotherapy and radiation treatments for cancer. Raloxifene is the active ingredient in Evista®, Eli Lilly's product for osteoporosis which uses a different solubilization technology. Rivastigmine is the active ingredient in Exelon®, the Novartis drug for management of Alzheimer's disease. Risperidone is the active ingredient in Risperdal®, Janssen, L.P.'s product for the management of schizophrenia and bipolar mania.

We plan to continue to seek additional alliance and partnership agreements, while we advance our internal and existing partnered development portfolio. We intend to leverage the expertise and the established infrastructure of our partners for certain product applications as we advance and expand our own product pipeline and broaden our intellectual property position. ◆


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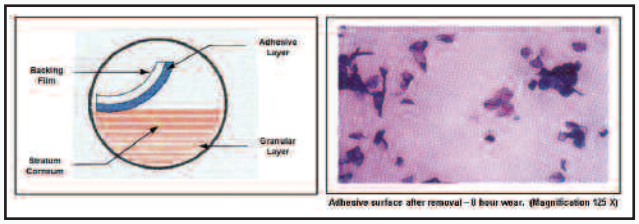
Technology Showcase

Adhesive Technology



Conventional transdermal technology has relied upon traditional pressure sensitive adhesives, which include primarily acrylate, silicone, and rubber or polyisobutylene-based polymers as the primary matrix to adhere the patch to the skin. With these traditional adhesive types, a significant amount of stratum corneum cells are removed and transferred to the adhesive surface, resulting in damage and irritation to the skin. The technology employed by Aveva and Nitto Denko is based upon a proprietary adhesive composition that addresses these problems. This Gel-Matrix adhesive has unusual properties that allow for exceptional adhesion and wear to the skin without the removal of a significant amount of stratum corneum cells. This allows for unique properties, including the ability to reapply patches while reducing skin damage and irritation. For more information, contact Robert Bloder at (954) 624-1374 or visit **www.avevadds.com.**

Contract Services

Azopharma
Contract Pharmaceutical Services

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Pharma Development Services

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Technology Showcase

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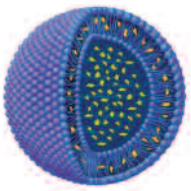
Nanolipidic Particle Technology

dermaCM
FDA Registered Contract Manufacturer



dermaCM offers proprietary nanolipidic particle (NLP) technology in taste-masking applications via license agreements or contract manufacturing of beverage, pharmaceutical, and nutraceutical preparations. The process is safe and all-natural, offering manufacturers consumer acceptance, patient compliance, and user satisfaction advantages. These NLPs feature high-loading capacity of passenger molecules, clear appearance, control of population size, a 60- to 150-nm range, and are inherently non-precipitating. dermaCM provides this NLP delivery system along with other proprietary nanosphere delivery systems for OTC pharmaceutical, beverage, nutraceutical, and dermatological applications. dermaCM also offers formulating, private labeling, manufacturing, packaging, and fulfillment services supported by stringent adherence to FDA regulations for OTC pharmaceuticals and respected industry standards for cosmeceuticals. For more information, contact Robert Dowdell at rdowdell@dermazone.com or visit **www.dermacm.com.**

Iontophoresis Technology

EyeGate Pharma is pioneering the use of iontophoresis to safely and non-invasively deliver therapeutics to tissues in the front and back of the eye. EyeGate is developing its proprietary drug delivery system, the EyeGate® II, as a patient-friendly, non-invasive alternative to current ocular delivery modalities, such as eye drops, which are largely ineffective, and intraocular injections or implants, which can lead to safety issues. The system employs a mild, applied electric field to enhance the transport of specially formulated molecules into tissues throughout the eye. EyeGate is building its proprietary internal therapeutic pipeline while quickly becoming the ocular delivery partner of choice for drug development companies. For more information, contact Remis Bistras at info@eyegatepharma.com or visit **www.eyegatepharma.com.**

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SPECIALTY PHARMA
Strategies For Business Development

Analytical Services

Analytical Laboratories: Trends, Management & Relationships

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

Introduction

A new report from the Indianapolis-based research company BioCrossroads indicates the overall contract service provider market is valued at approximately $14 billion and growing at 14% to 16% annually. Some of the services experiencing especially high demand in this market are early phase activities, such as analytical chemistry, toxicology, and other preclinical services, as well as Phase I clinical services. Analytical methods are critical in PK, PD, and ADME studies. Service providers that offer analytical testing are essential to the drug discovery and development process. The analytical market alone, according to BioCrossroads, is a $12-billion market. *Specialty Pharma* magazine recently asked several of the industry's leading analytical laboratories about trends in the sector, project management, and how Specialty Pharma companies can best manage relationships with providers. Participants include Jim Baker, Manager, Quality Control Laboratories, Norwich Pharmaceuticals; Matt Duggan, Analytical Services Manager, InB:Hauser Pharmaceutical Services, Inc.; Phil Meeks, PhD, CEO, Azopharma, Inc.; and Frank Santillo, PhD, Senior Director of Research Services, Bilcare Global Clinical Supplies, Americas.

Q: ***To begin this discussion, is there anything our readers should know about the current state of affairs regarding the analytical testing services sector?***

Dr. Meeks: We are seeing an increase in the amount of early development work currently being outsourced. Traditionally, firms had a tendency to outsource quality control and stability services for Phase III or commercial products. While this is still happening, firms seem to be going further back in the development cycle and looking for analytical activities that can be outsourced.

Dr. Santillo: Several advances have made significant impact on the status of analytical methods. Techniques are becoming more sophisticated. The methods evolve in part due to the increased demands from both Drug Discovery and Drug Development. Existing technologies are being combined to provide more/better information. Hyphenated techniques, such as MS-MS, ICP-MS, and CE-MS are available. Miniaturization advances have impacted the selection of APIs and have also provided new techniques. APIs that had previously been shelved due to low solubility are now being studied because nanotechnology has made these drugs usable again. And with the milling of APIs to nanometer-size particles, particle-sizing methods have been developed to measure the nano-milled drug substance. Microfluidics, another new field, has proven to be useful in scaling down reaction vessels. Stereochemistry is steadily increasing in importance in the development of new drugs. Chiral purity information can make therapy safer and more efficacious. Analytical technology has responded with several means of chiral discrimination. The most familiar approach to measuring chiral purity is chromatography. Enantioselective biosensor technology is a new area that has developed to respond to the need of establishing enantiomeric purity.

Mr. Baker: Simply speaking, there are more services that are more readily available from a larger number of suppliers than ever before. There are both specialized and broad-scope laboratories available to support every niche and need of the pharmaceutical industry. Additionally, new technologies and "high-end" analytical techniques, which have traditionally been reserved for large institutions in their captured facilities, are continually becoming available and affordable and are pouring into the contract testing industry. Every contract laboratory from large to small offers a different set of specialties, capabilities, and services that create unique experiences for customers. When shopping for analytical testing services, it is important to consider your needs in relation to the overall experience the contract lab will deliver. It goes without saying that the laboratory must possess the technologies and capability necessary to meet your needs. However, the intangible factors, such as individualized service, complementary culture, transparency, diplomacy, and open mindedness to your ideas, will be major contributors to your overall satisfaction.

Mr. Duggan: Analytical chemists are increasingly challenged to develop a broader range of analytical skills as a result of new and emerging pharmaceutical technologies, including but not limited to, biologics, drug delivery, prodrugs, Specialty Pharma, personalized medicine, and diagnostics. All of these changes are exciting technological developments on the frontier of modern medicine and will have profound effects on the analytical services sector. Today, analytical chemists are asked to develop and characterize methods and perform routine testing on a variety of different actives, grouping of actives, impurities, and formulations. Whereas in the past most actives tested and developed were small molecules, today, an increasing number of new drugs are large molecules, eg, proteins and peptides. Likewise, instead of working with a single isolated compound, analytical chemist's are increasingly asked to work with a more complex grouping of larger more complex molecules consisting of actives, targeting compounds, linkers, etc.

Q: ***Throughout the past several years, what trends have you noticed with regard to the types of analytical services clients are seeking?***

Mr. Baker: Rather than seeking a new type of analytical service, Norwich clients are asking for a new type of client-contractor relationship. The work at a contract laboratory can mean the difference between the success and failure of a project. Additionally, the work performed at contract labs must be considered in the overall regulatory risk profile for the sponsor. Naturally, Norwich sees clients proactively seeking to understand and control their risks. We see our clients seeking relationships in which Norwich works as an extension of the client's own organization. Many clients are seeking cooperative relationships in which we are not simply contracted to provide a black box service. Rather, Norwich is asked to perform as if we were a work team within the client's own company. To meet these new expectations, we provide our clients with unprecedented transparency into our organization. As a contractor, we drive the work while maintaining alignment with the client at every step.

Mr. Duggan: New analytical technologies that enable companies to get to market quickly at reduced costs are driving trends toward increased sample automation and faster resolution equipment, such as UPLCs, LC/MS/MS/MS, and high-resolution NMRs. While we expect the trends in this direction to continue, access to these new

technologies can also present a catch-22 for companies. Although these better analytical techniques present more precision and differentiation, they can also present issues when previously undetected compounds are now discernable. We also often find some trends come and go. Companies, for example, often seek analytical support in response to new regulations or when a particular aspect of drug quality receives increased regulatory scrutiny. A few years ago, extractables and leachables received considerable regulatory attention and as a result, there was a spike in the number of companies seeking contract extractables and leachables testing. Consequently, this trend has decreased as many firms are now performing that testing internally.

Dr. Santillo: As drugs become more potent, there are much smaller amounts of active per dose. So the detection levels for a method must decrease to meet these levels. Impurities, which may be present in a product, are generally found in tenths of a percent relative to the active content. Thus, the detection level for the impurities in a potent drug product becomes an even more challenging goal. Methods today need to be able to accurately and precisely quantitate components in a complex mixture to ppm levels on a routine basis. There is also a push to obtain results with increased speed. In drug discovery, high-throughput screening has become a powerful tool for filtering the thousands of compounds resulting from programs, such as genomics. And to meet the increasing speed of analysis, there is the corresponding speed of reporting results. Thus, with high-speed connectivity, web-based reporting mechanisms have surfaced. Clients are able to query a website of the contract laboratory to obtain up-to-the-minute results of their submitted samples.

Q: ***What should Specialty Pharma clients expect in terms of project management from an analytical testing provider?***

Dr. Meeks: Project management functions should focus on the communication of results to clients and management of the project timelines. At times, project managers tend to try to be the holder of all the information. We believe this approach is not as efficient or effective as having the project managers facilitate the one-on-one discussions between the pertinent scientists from the firm and the outsource provider.

Mr. Duggan: Pharmaceutical companies should expect proactive project management for their analytical projects. Communication is the essential element for the overall relationship. Before starting any work, InB:Hauser reviews with the client various assumptions made in a proposal to make sure the proper goals, scope, budget, and timeline of the project have been identified and agreed upon. Subsequent to starting a project, a pharmaceutical client should expect its analytical project manager to provide prompt, detailed reporting of any problems the lab might encounter. Following this, project managers should make every effort to enter into a reciprocal solution-focused dialogue with clients as how best to proceed to ensure critical decisions made by the client are not made in a vacuum. Finally, any changes in scope, budget, and timing need to be immediately communicated and resolved with clients before additional work is done.

Mr. Baker: The project management services available vary as much as the differing client needs. Clients should expect a level of project management commensurate with the complexity of the overall project scope. The requirements may vary from simple management of a single study to the management of full-scope development projects. The management needs should be evaluated and defined during the sourcing stage of the project. Clients should evaluate a service provider's project management capabilities during the process of selecting a contractor. Regardless of scope, strong project management services are key to delivering on time and on budget.

Dr. Santillo: In many situations, the manner in which the project is managed is the key to its successful execution. Project Management (PM) should provide a project plan so the client knows what to expect and when to expect it. The PM should also provide up-to-date status reports to the client in a proactive manner. They should work with the technical staff on their team to assess the potential risks of the project and construct appropriate back-up plans that would address each risk. Bilcare prides itself in providing Project Managers that have extensive training in project management. A Bilcare Project Manager is assigned to every client. The PM carefully constructs a project plan, which has input from each pertinent department. The PM also acts as a central point of contact and manages the communication and needs between the two facilities.

Q: ***When seeking an analytical testing provider, when is it more beneficial to choose a "one-stop-shop" that provides every service or focus on a task-specific provider?***

Dr. Meeks: In early clinical development, a firm can save substantial time by outsourcing to a single provider that has full product development capabilities. By outsourcing to a single provider, a firm does not have to manage multiple contacts, transfer material or data between organizations, or familiarize a new provider with their compound. Time is crucial in early development and in getting a go or no-go decision for further clinical development.

Dr. Santillo: Time is the biggest factor in deciding on a one-stop-shop. When all the testing being conducted is located at a single facility, there are no hand-offs between laboratories. By eliminating the hand-offs, time is saved. However, some situations require a significant level of depth for a specific test. The appropriate laboratory is one in which there is demonstrated expertise in the desired field. Instrumentation for the desired test is research grade, and there may be several instruments of that type. Analysts may have advanced degrees in the field of interest.

Mr. Baker: In a basic sense, a one-stop-shop can be any contractor that can meet all the tasks of a given project. Depending on the project scope, this may not necessarily be a large laboratory with a vast array of capabilities. A one-stop-shop need only have the capability to provide the full scope of your project and possess reasonable ability to meet unexpected needs either through internal resources or by subcontracting to strategic partnering labs. For example, Norwich Pharmaceuticals' business is contract manufacturing. Our laboratory rounds out the one-stop service for the vast majority of our clients by providing quality control, stability, and

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microbiology testing services. If the need arises for service outside our capability, Norwich can work with our approved contractors to provide seamless coordination. A task-specific provider is best used when there is a single specialized need, such as a specific technology, expertise, problem to be solved, or consulting requirement. In these cases, the importance and sometimes urgency of the specific need outweighs the need for convenience of a one-stop-shop.

Mr. Duggan: Clients bringing new products to market should look for CROs/CMOs that can conduct as much of the analytical testing as possible under one-roof. This ultimately minimizes costly time-consuming hand-offs, and allows for efforts to move along more quickly and efficiently. The benefits of using this approach range from raw material, in-process, and analytical release testing in support of a contract manufacturing project to formulated product stability testing. The one-stop-shop will provide consistent experience and applies principles and techniques that result in coherent analytical results to support regulatory filings as well as lot-to-lot consistency. Unfortunately, finding a full-service provider that can work with the wide variety of today's complex compounds is not easy to find. On the contrary, most CROs/CMOs appear to operate in increasingly specialized niche markets. Task-specific providers may provide essential assistance to the completion of any pharmaceutical project, particularly those projects still in development. Certain analyses require rare or unique capabilities. For these types of testing, a task-specific provider is the most economical and efficient option and would provide assistance in data interpretation. Most pharmaceutical products will require some specialized analytical technique for early characterization that may not be needed for routine product release testing.

Q: ***From your perspective, what should Specialty Pharma companies do to better prepare themselves for a new relationship with an analytical testing provider? Basically, how can they avoid the most common mistakes?***

Dr. Duggan: The most common mistake is to believe that any of this work will be easy. In our experience, we have developed and worked with hundred's of analytical methods for our clients, most of which customer's initially thought were robust. Changes to your process can require subsequent changes in your analytical testing methods, all of which is more dynamic than customers typically assume. In the end, identification and implementation of robust analytical methods, which consistently produce results from batch to batch, is difficult. It is usually mutually beneficial, although often difficult, to learn from a contract analytical laboratory that methods provided to the contract laboratory are not working as expected. Pharmaceutical companies that can accept a failed method transfer and are willing to work with the contract laboratory will usually obtain a satisfactory resolution to the problem in a reduced amount of time. The free flow of information between a drug sponsor and contract analytical laboratories is a critical component of the relationship between the companies. Another common mistake is to get into later stages of development only to find you are looking at your product incorrectly. The quicker clients develop a robust analytical methods the better. Finally, take advantage of all the experience and expertise your analytical lab has to offer. In order to achieve the most effective relationship, a company should share as much existing knowledge about a product or analysis with the contract analytical laboratory. Arming the analytical laboratory with comprehensive information about a product helps minimize the time and cost of method transfer or even routine analysis. For early development, a products background information may not be available. However, providing any existing information about the product eliminates "reinventing the wheel" and streamlines method optimization.

Mr. Baker: From my perspective, one of the most common mistakes early in a relationship is the shortage of communication due to presumed alignment in expectations. Most of us are successful at working within our own company. When working within one's own company, one operates within a complex set of implicit instructions. These implicit instructions are simply understood as, "the way we do things here," and followed by all employees of that company every day. The problem arises when the two sets of implicit instructions held by the contractor and client don't match. At the beginning of a relationship, they never do, and both parties need to be aware of that and prepare for it. When starting a new relationship, make no presumptions. The client has a vision of what it wishes to receive, and the contractor has a vision of what it's going to deliver. At the beginning of a relationship is the time to concentrate the communications on sharing, understanding, and aligning those visions. The communication should extend beyond simply aligning on the project goal and deliverable. The communication should be focused on bridging the gap between the ways the two companies would approach the same problem. Focus should be spent on turning the two sets of implicit instructions into a detailed understanding of the specific expectations at each stage of the project.

Dr. Santillo: To ensure a client and a contract analytical laboratory have a successful relationship, there needs to be a concerted effort on both parties to make the relationship work. The client should conduct its due diligence. Pertinent questions the client should ask the laboratory are: 1) Does the laboratory have detailed and current SOPs and an effective quality group?; 2) Has the laboratory been successfully audited by the FDA recently?; 3) Does the laboratory have the instrumentation and the level of expertise needed for the project?; and 4) Is it possible to discuss data directly with the analysts working on your project? Equally, the laboratory should ensure it completely understands the scope of the work being requested. It should provide a reasonable estimate of the timing for the work. And most importantly, the laboratory should keep the client involved throughout the project with updated status reports.

Dr. Meeks: Communicate. Let the expectations be known up-front as far as communication, science, quality, etc and be open to developing a partnership with the outsource provider rather than viewing the outsource provider merely as a contractor.

Q: ***In your opinion, what should your clients (our readers) know about the future of the analytical testing industry as it relates to them?***

Dr. Meeks: Analytical chemistry will always be the means by which product performance and quality is determined. Embracing emerging technologies that increase the accuracy and precision of

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such determinations will also enable analytical laboratories to reduce analytical timelines which in-turn can reduce costs. Quality, timelines, and price are the three most important factors most firms consider when selecting and partnering with a provider or performing analytical functions. Thus, firms and outsource providers should not shy away from new technologies simply because they may not represent the traditional ways of performing the testing.

Dr. Santillo: Analytical testing has assumed a more prominent role in the drug development process. Involvement of the analytical laboratory should be obtained early into the program. A strategy should be put in place to establish methods early and to characterize the lead candidate. Questions related to measuring related substances at ppm levels need to be considered. Experience gained on a set of methods may be leveraged when testing the drug product. Overall, a well-characterized API and an established set of methods created early in the development program will minimize hurdles later in the development process and provide a much more sound understanding of the product.

Mr. Baker: The contract industry as a whole is growing, and all indications are that the growth will continue. Even big pharma companies are increasingly leveraging the capabilities of contract labs. Additionally, there is a shift from using contractors to simply fulfill tactical needs to models in which clients are incorporating contractor use into their strategic plans. In either case, there is a growing expectation that contract laboratories operate like an extension of the client's own organization. All this translates into better service for Specialty Pharma companies. Ultimately, the move toward strategic relationships is providing stability to contract organizations. It is allowing contract organizations to acquire new technologies and capabilities that focus on the needs of Specialty Pharma companies. Also, with the shift to strategic relationships and the expectation that contractors operate as an extension of the client's lab, clients will have greater visibility into the contract organization. This transparency will translate into better working relationships, lower risks, greater responsiveness, smoother projects, and ever-increasing satisfaction.

Dr. Duggan: As a result of the expanding world of pharmaceuticals, actives, new drug delivery, biologics, and personalized medicine products, and many similar technologies, there will be an increasing distinction between the analytical labs offering a very broad set of highly diversified skills and capabilities versus the labs who offer a very narrow targeted set of skills and capabilities. The analytical labs that offer a broader depth and breadth set of capabilities will be a more useful partner in the development of new biologics, drug delivery technologies, personalized medicines, diagnostics, and other similar market segments. The analytical testing industry will remain committed to providing high-quality results compliant with regulatory guidelines to their pharmaceutical customers. Testing laboratories must stay current with the ever-changing regulations and provide testing as economically as possible. As pharmaceutical development costs continue to soar, the outsourcing of various analytical projects to research-oriented contract laboratories will grow accordingly. Contract analytical testing services are an efficient, cost-effective option for pharmaceutical companies to consider. ◆

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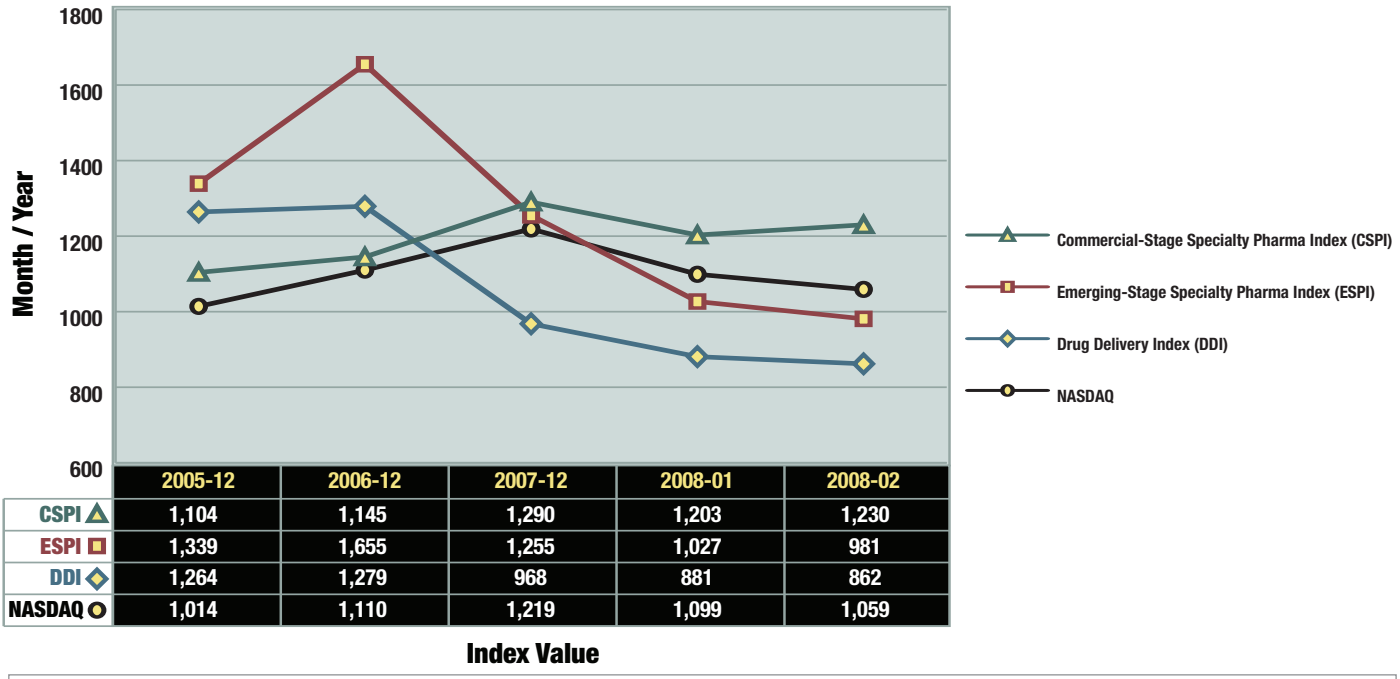
Facts & Figures

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

Bionumbers Composite Index



	2005-12	2006-12	2007-12	2008-01	2008-02
CSPI	1,104	1,145	1,290	1,203	1,230
ESPI	1,339	1,655	1,255	1,027	981
DDI	1,264	1,279	968	881	862
NASDAQ	1,014	1,110	1,219	1,099	1,059

Index Value

CSP Index Value: 1230 | Change YTD: -4.6% | Change M/M: +2.3% | Total Index Capitalization: $91.2 Billion

Top 5 Capitalizations YTD Change		
Shire	$11.0 Billion	-14%
Hospira	$6.4 Billion	-5%
Warner	$4.2 Billion	-5%
Endo	$3.6 Billion	0%
MGI Pharma	$3.4 Billion	+3%

Top 5 Gainers YTD Change	
Middlebrook	+227%
Encysive	+166%
Collagenex	+32%
Valeant	+16%
Pharmion	+12%

Top 5 Laggards YTD Change	
Barrier	-33%
Santarus	-31%
Indevus	-25%
Medicis	-25%
Salix	-20%

ESP Index Value: 981 | Change YTD: -21.9% | Change M/M: -4.5% | Total Index Capitalization: $2.7 Billion

Top 5 Capitalizations YTD Change		
Nektar	$578 Million	-7%
PainTherapeutics	$399 Million	-15%
Durect	$364 Million	-24%
Keryx	$240 Million	-35%
Cadence	$221 Million	-49%

Top 5 Gainers YTD Change	
NovaDel	+75%
Epicept	+19%
Sonus	+8%
Acusphere	+5%
Antares	+3%

Top 5 Laggards YTD Change	
Penwest	-52%
Cadence	-49%
Elite	-43%
Keryx	-35%
Alexza	-25%

DD Index Value: 862* | Change YTD: -11.0% | Change M/M: -2.2% | Total Index Capitalization: $9.7 Billion

Top 5 Capitalizations YTD Change		
Biovail	$2.2 Billion	+2%
Alkermes	$1.3 Billion	-18%
Surmodics	$792 Million	-21%
Eurand	$596 Million	-14%
Nektar	$578 Million	-6%

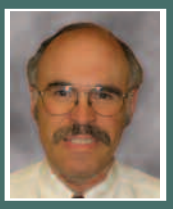
Top 5 Gainers YTD Change	
Labopharm	+110%
NovaDel	+75%
Acura	+34%
Bioject	+14%
NexMed	+12%

Top 5 Laggards YTD Change	
Vyteris	-59%
Penwest	-52%
Nastech	-47%
Elite	-43%
Emisphere	-32%

* December 31, 2004 value set at $1000

Executive Summary

Dr. Ronald Ellis
Senior Vice President, Chief Technology Officer
NasVax



NasVax: Improving Vaccines With a Unique Platform

By: Cindy H. Dubin, Contributor

NasVax is engaged in the development of vaccines based on its VaxiSome™ platform for improving the immune response to vaccines and enabling both injection and intranasal administration. VaxiSome utilizes CCS/C, an adjuvant and delivery system shown to stimulate increased antibody responses as well as T-cell responses. This opens the way for developing further product applications for preventing or treating infectious and non-infectious diseases. The company's lead product is in Phase I/IIa clinical studies, and NasVax has a joint development agreement with SciGen Ltd to develop an improved Hepatitis B vaccine based on VaxiSome. The company is in initial stages of developing improved vaccines to prevent avian flu and anthrax and is considering the in-licensing of novel antigens for internal development of new vaccines. VaxiSome is based on research by Professors Eli Kedar and Yechezkel Barenholz, co-inventor of a liposomal formulation of doxorubicin for cancer treatment, marketed in the US by Johnson & Johnson (as Doxil™) and in Europe by Schering Plough (as Caelyx). Dr. Ronald Ellis, Senior Vice President and CTO, and a leader in the field of vaccine and biologics development, recently spoke with *Specialty Pharma* magazine about how the company has built up its management team since its founding in 2004 by the Meytav Technological Incubator in Kiryat Shmona; completed two private investment rounds that same year; and had a successful IPO in 2005 to become a public company traded on the Tel Aviv Stock Exchange.

Q: ***What need did NasVax set out to meet in the marketplace in 2004?***

A: Influenza is one of the major causes of mortality (300,000 to 500,000 per year) in the developed world, especially among the elderly. The expected worldwide sales for flu vaccines in 2007 are approximately $2.5 billion, which is expected to reach around $5 billion by 2016. The biggest challenges for vaccine companies in this field are the development of improved vaccines for preventing flu as well as increasing the number of responders, especially among the elderly who often do not respond well to the existing vaccine. Other challenges include cutting the dosage level of vaccine in order to extend the world's supply of vaccine and providing an alternative method of administration, which can be done by nasal spray. This method can serve people who cannot receive or do not wish to receive an injection and allows for possible independent use by the subject. Almost all new vaccines (besides live vaccines) require adjuvants to enable them to be immunogenic enough to effectively prevent or treat diseases. In addition, new vaccines benefit

from being delivered by routes other than injection. NasVax provides a novel adjuvant/delivery system that has been shown to not only stimulate an increased antibody response but also produce a cell-based response and thus further improve potency. This potent system opens the way for developing further product applications for preventing or treating both infectious and noninfectious diseases, and can also promote a reduction in the number of doses or in the dosage level needed to achieve a protective response.

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

A: The company's VaxiSome core technology provides activities of both an adjuvant and a delivery system. Both of these activities can enhance prophylactic and therapeutic vaccines. This means that the adjuvant activity can augment the immunogenicity and protective effect of a prophylactic vaccine as well as the ability of a therapeutic vaccine to prevent progression or reverse the pathology associated with certain chronic diseases. There are relatively few such technologies that have this sort of dual activity.

In addition, NasVax is a small, highly focused company in a growing sector of biotechnology. Having only 13 employees, the company relies extensively on outsourcing activities to contract research and contract manufacturing organizations. This means that much of the time of internal staff is invested in selecting excellent outside organizations and working closely with them to assure they meet the company's goals. This deployment of external resources enables the company's staff to leverage their skills, make rapid decisions, and get much more work accomplished than a staff of 13 would normally be able to achieve. There are relatively few vaccine companies that are as small as NasVax yet have leveraged their resources to work on multiple projects as effectively as the company has done to date.

Q: ***Please describe how the VaxiSome platform works?***

A: The VaxiSome platform technology is based on cationic lipids that form liposomes — these bind to vaccine antigens and present them in a highly concentrated fashion to cells of the immune system, thereby stimulating potent antibody- and cell-based immune responses. The positive charge of the VaxiSome particles naturally attracts the antigen molecules in the vaccine formulation to such cells.

VaxiSome is a liposome, which is a small lipid particle. The vaccine antigen is mixed with these particles, which takes up the antigen internally and also presents the antigen on its surface. These particles then can bind to certain cells of the immune system, which in the case of a prophylactic vaccine, recognize the antigen very efficiently as foreign to the body, thereby leading to a strong stimulation of the immune system to produce both antibodies and cells that are specific for recognizing the foreign antigen. In the case of influenza vaccine, presentation of the vaccine antigens by VaxiSome leads to a strong immune response to the influenza virus, thus preventing clinical disease.

In addition to such adjuvant applications, VaxiSome can enable nasal delivery of antigens, resulting in the stimulation of a mucosal immune response that can prevent infection at a mucosal site where the pathogen enters the body. This route of delivery also can be a desirable alternative for those who prefer to avoid vaccination by needlestick. Moreover, in therapeutic applications, there can be a stimulation of the immune response to a molecule that is involved in the pathogenic process, thereby resulting in a remission or reversal of the disease process.

Q: ***What types of companies are attracted to the platform, and how are they using it?***

A: This type of technology is useful to companies that specialize in prophylactic vaccines as well as those that are active in developing therapeutic biologicals that stimulate immune responses. Both large companies with broad portfolios as well as small companies with one or two products have found this type of technology attractive. Initial collaborative investigations are carried out in animal models followed by clinical studies.

When we look broadly at the field of vaccines, we can see how adjuvant technology has become much more widely employed with new vaccines. Until approximately 10 years ago, the only licensed adjuvants were aluminum salts, which have been used in billions of doses worldwide throughout the past 5 decades. It was realized that optimizing the immunogenicity and efficacy profile of new vaccines would require the use of more potent adjuvants, which spawned a new era in adjuvant research and development. As a result, there have been three new adjuvants licensed for commercial vaccines throughout the past 10 years. The increased comfort of companies, clinical researchers, and regulatory authorities in evaluating new adjuvants has led to an increasing number of adjuvanted vaccines being evaluated in clinical studies, which have been sponsored by both large and small companies. Beyond the large number of prophylactic adjuvanted vaccines in development, most therapeutic vaccines employ an adjuvant to ensure strong immunogenic activity. An increasing number of large pharmaceutical companies have undertaken programs with therapeutic vaccines, many through partnerships with smaller companies.

Q: ***What else are you doing to enrich your pipeline? Are you looking at in-licensing/out-licensing opportunities with other companies?***

A: We are working toward licensing in novel antigens for internal development, in addition to establishing development partnerships, such as the one recently set up with SciGen for the development of improved Hepatitis B vaccines. We can employ our technology in two ways. One is to adjuvant existing vaccines or to enable nasal delivery. To these ends, we look for partner companies with available vaccines or vaccine antigens that would benefit from increased immunogenicity or from nasal delivery to stimulate a mucosal immune response at the site of infection. We would then work with the partner company to develop processes and assays for combining antigen and VaxiSome for both preclinical and clinical studies. Such collaborative work would take place both at NasVax and at the collaborating company — most of the work would be expected to be undertaken by the partner company in such cases, hence somewhat more an out-licensing with appropriate rights and benefits to NasVax.

The second is to acquire antigens from small companies or universities/research centers. Such antigens can be combined with VaxiSome in order to increase their immunogenicity or to enable nasal delivery. These candidate vaccines would be developed by NasVax and brought through preclinical and clinical studies. NasVax seeks antigens for both prophylactic as well as therapeutic applications. In the latter case, the company may work with a large pharma/biopharma partner for late-stage development. Either of these models of projects and collaborations could be applied to developing new prophylactic or therapeutic vaccines.

Ultimately, we seek to develop internal vaccine candidates as well as to establish VaxiSome as an enabling technology with partners for the development of both prophylactic and therapeutic vaccines for infectious diseases as well as non-infectious chronic diseases. We will be planning to reach late stages of development or commercialization for one or more of these vaccines. ■

The Challenges of Medical Diversity

By: Udo Kiessling, MD, PhD, Corporate Vice President & Worldwide Head of Medical Affairs, Clinical Research Services, PAREXEL International

Introduction

The development of new medicinal products is guided by internationally accepted principles and practices in the conduct of both individual clinical trials and overall development strategies starting from drug discovery, lead identification, and preclinical testing all the way through the clinical phases of development and drug approval. The major aim of this highly regulated process is to prove efficacy of new medicines and ensure patient safety throughout development and commercialization.

Drug development continues to be inherently challenging, with recent figures indicating that less than 11% of new pharmaceutical agents entering clinical development reach the marketplace, no matter whether those are new chemical/molecular entities or biologics. Although a number of approaches to increase the probability of success in drug development have been investigated, the cost and duration of getting new medicines to market remain high, and the success rates are unchanged. The Tufts Center for the Study of Drug Development has estimated that the cost of developing a new drug is in the range of $800 million to $1 billion and takes an average of 8.5 years.

Drug developers and other stakeholders in the biopharmaceutical industry, including regulators, owners of health expenditures, policy makers, and patients are increasingly concerned about growing healthcare spending in aging societies. Changes in the demographic structure are heralding increased incidences of neurological disorders, cancer, and cardiovascular diseases, which put additional pressures on the development of affordable medicines. In recent years, we have also seen an unprecedented interest in patient safety and the quality of healthcare. The call for new, safer, and more efficacious medical products is steadily increasing, particularly for the elderly and pediatric patient groups.

Most medicines are currently prescribed empirically, based on practical medical experience. However, recent advances in understanding the mechanism of underlying diseases and drug responses, as well as adverse drug reactions, are increasingly creating opportunities to match patients or groups of patients with therapies they are more likely to respond to in a safe and effective manner.

The complex nature of drug development is now well recognized and is mainly due to the heterogeneity and nature of the underlying disease in a patient population. This poses the question whether different therapeutic areas and various diseases require a specific approach in drug development. Interestingly, there are key differences among major therapeutic areas with regard to success rates in clinical development. Oncology and central nervous system (CNS) drug discovery have poor records for investigational drugs in clinical development as compared to cardiovascular drugs. The drug development success rate in oncology (5%) and CNS (7%) is more than three times lower than in cardiovascular development (20%). The therapeutic areas of oncology, cardiovascular, and CNS share a number of factors. All three are characterized by high incidence rates and affect large parts of the population, particularly in Europe and North America, with clear signs of increase in the Asia-Pacific region. These areas of specialized medicine are putting increasing burdens on the global healthcare expenditure, and despite decades of research and development, still contribute significantly to morbidity and mortality rates.

The drug development process follows an international consensus framework, as outlined primarily by the International Conference of Harmonization (ICH) guidelines and the Council for International Organizations of Medical Sciences

(CIOMS), consequently adapted into regulations by health authorities. With the common scheme of the development process in mind, all steps of the process bear a potential for differences among these major therapeutic areas, resulting in different success or alternatively various attrition rates. Differences can be assumed at the level of 1) discovery (lead identification/optimization); 2) preclinical testing (disease models for efficacy and animal toxicology/pharmacology); and 3) throughout the entire clinical phase of development (choice of trial design, patient population/control groups and definition of primary outcome measures). Throughout all stages of drug development, differences in the knowledge about pathophysiology and the natural course of the disease will have a potential impact on strategic decisions and thus final outcomes.

Comparing cardiovascular (CV), CNS (including neurology and psychiatry), and oncological diseases, there seems to be obvious differences with regard to the availability of appropriate animal models and their predictive value, validated biomarkers, and surrogate markers to guide clinical development. There are also differences concerning the definition of primary outcome in clinical trials. Ideally, the outcome of a clinical trial is defined as the clinical benefit of the investigational drug in comparison to a control group. The demonstration of clinical benefit as a variable to measure how patients feel, function, or survive largely depends on the method used to establish this benefit. This assessment could be based on objective tests or subjective descriptions, such as performance scales or even patient reported outcomes. In CV drug development, the primary outcome is mostly related to a clinical benefit expressed by improvements of mortality rates or surrogate markers, such as blood pressure control, electrocardiogram (ECG) normalization, or reduction of lipid concentration. Most surrogate markers in cardiology were proven to be predictive for a clinical benefit (eg, improved survival, in large clinical trials).

A clinical benefit is more difficult to establish in some types of cancer trials, in particular, in tumor entities with long progression-free intervals, and is regarded as almost impossible. In some CNS diseases, where the demonstration of a clinical benefit might require patient follow-up in clinical trials for 10 or more years, this is not feasible under both economic and ethical considerations.

Cardiovascular Diseases

Incidence and prevalence data indicate that cardiovascular diseases globally remain a significant challenge contributing to overall morbidity and mortality rates observed in most of the developed countries. Nevertheless, incredible advances have been made in diagnosis, treatment, and prevention of cardiovascular diseases during the past half century. Evidence-based medicine to a large extent has contributed to the development of efficient therapies and procedures in the treatment of myocardial infarction, hypertension, and congestive heart failure. As a significant difference to CNS and cancer, in cardiovascular medicine, considerable knowledge about pathophysiological mechanisms and environmental- and life style-related risk factors has been accumulated, providing good guidance in drug development. As a result, the success rates are among the highest in drug development. The understanding of the underlying mechanisms and the complex nature of the disease support the choice of the right drug target, addressing a relevant physiological pathway and the best possible timing of the intervention. The profound knowledge of disease and the potential mechanism of intervention also translates into the choice of the right subjects or subgroups of subjects in CV clinical trials. Better knowledge of the mechanism of action enables the drug developer and the investigator to identify a well-defined group of patients likely to respond to an intervention, and therefore most likely resulting in an improved clinical outcome. The development of treatments for acute myocardial infarction, such as thrombolysis and PCI together with the administration of ß-blockers, ACE inhibitors, and platelet aggregation inhibitors, resulted in a major improvement of clinical outcome. However, subtle difference between available standards of care and new treatments in CV drug development require clinical trials larger (often 10,000+ patients) than in any other therapeutic areas to reach results with statistical significance.

The existence of proven surrogate markers as mentioned earlier is providing a clear advantage in CV drug development compared to CNS and cancer. However, this is true only for well-understood disease modalities. The difference is smaller in areas of cardiovascular development in which underlying pathogenetic mechanisms are not known in detail. In recent years, attempts were made to reduce post-MI reperfusion injury, a major risk factor of unfavorable outcomes. Most of the trials so far failed to show a significant benefit of treatment versus placebo. Therefore, the complexity of the pathophysiology of the myocardium post-MI and the (limited) understanding of the pathogenesis appear to be important drivers toward therapeutic success or failure. Available biomarkers, suitable animal models, and a better understanding of pathogenesis in CV diseases do seem to increase predictability of clinical outcome and overall success in drug development. Nevertheless, even three-fold higher success rates when compared to CNS and oncology drug development, an 80% failure rate remains challenging and encourages further improvements.

Central Nervous System Diseases

In CNS drug development, only about 7% of drug candidates reach the market. CNS treatments take an average of 12.6 years to develop, compared to 6.5 years for cardiovascular indications. Despite many decades of effort, the progress in developing new therapies for neurological and psychiatric disorders has been somewhat disappointing and unsatisfactory. Disorders of the CNS are among the most prevalent, devastating, and yet poorly treated diseases. Most existing treatments are symptomatic and do not affect the underlying cause of the disease. There are a number of reasons making CNS drug development so challenging, beginning with the complexity of the brain itself. The blood-brain barrier (BBB) adds a degree of uncertainty in predicting CNS drug pharmacokinetics and pharmacodynamics, particularly due to changes in permeability and function recognized in a number of neurological conditions. A further complication is the lack of validated biomarkers to understand whether a given neuro-therapeutic agent is reaching the brain in concentrations sufficient to modulate the desired target. The limited understanding of disease mechanisms and pharmacological action has impeded discovery of more effective therapies. In addition to the previously discussed reasons to explain the challenges in CNS drug development, and the difficulties to translate experimental findings into clinical benefits, one of the more important is the lack of suitable *in vitro* and *in vivo* animal models, particularly models that address functional aspects of brain tissue, such as neuronal connectivity. The development of appropriate animal models with some predictive value is an obvious challenge in development of drugs for the treatment of psychiatric conditions. Adding to the complexity are the heterogeneous and, hence, poorly understood nature of psychiatric diseases, such as schizophrenia or depression, in addition to subjective rating scales to diagnose patients and measure primary outcomes in clinical trials. This poses the question of whether animal models addressing specific behaviors or symptoms of schizophrenia, dementia, or depression can be predictive at all. Current models rely on the assumption that the neuronal circuitry in animals somewhat mirrors that of human conditions, an assumption that is difficult to prove.

However, there seems to be some light at the end of the tunnel, The “omics” era has had considerable impact on target definition and selection, with more targets becoming available. This also opens up new avenues of drug development and allows for a new paradigm in CNS drug discovery and development based on defined molecular mechanisms and understanding of diseases. Because this approach had a positive impact on drug development for cardiovascular diseases, it seems likely that the same can be observed for disorders of the CNS. Conversely, the task of unraveling the pathophysiology of very complex, heterogeneous, and progressive disorders of the brain should not be underestimated.

There are other reasons for optimism – considerable progress is being made in the field of neuroimaging. Positron Emission Tomography (PET) and Magnetic Resonance Imaging (MRI) are playing an increasingly important role in drug development. Neuroimaging and related research are aiming to support the development of biomarkers that could allow the identification of sub-groups of patients more likely to benefit from treatment. In addition, it offers the potential for using biomarkers as surrogate endpoints for more timely and quantitative data collection than the traditional trial endpoints of morbidity and mortality. Neuroimaging applied to neurological and psychiatric drug development could help expedite and strengthen go/no-go decisions and thus positively impact cost and time to market.

Cancer Drug Development

Oncology, similar to neurology and psychiatry, also has a poor track record in clinical development and the lowest success rate overall when compared to the three therapeutic areas discussed here. Most factors differentiating drug development in oncology from cardiovascular development are reflecting the complexity of cancer biology. As, at the molecular level, two cancers are hardly identical, the resulting variety of diseases is perhaps wider than for any other area in medicine. The phenotypic manifestation of tumor heterogeneity is reflected in extremely different drug responses observed in clinical praxis. In patients diagnosed with histologically identical tumors, age, stage of disease, individual performance status, ethnicity, and many other factors have an impact on response and relapse rates as well as overall survival. It is well known that clinical toxicity and efficacy are difficult to predict from preclinical experiments or basic science. Cancer models similar to animal models in CNS diseases are notoriously unreliable, and it remains risky to advance compounds into clinical development on the basis of suppression of tumor growth in mouse xenografts. Subtle differences in cancer biology between patients may translate into significantly different anticancer activities of new compounds, considering the challenging complexity of cancer immunology, the role of dozens of cellular efflux pumps, various cell cycle checkpoints, and proliferation control mechanisms. Molecular research in oncology, however, has led to the identification of multiple new anticancer drug targets. Anticancer drug targets are commonly differentiated into those addressing essential versus non-essential functions. The inhibition of essential functions to kill tumor cells was historically the principle mode of action of cytotoxic drugs. It leads to on-target toxicity in normal cells and is reflected in

narrow therapeutic windows. The principle concern is on-mechanism toxicity, which clinicians and drug developers are trying to resolve by careful dose-response titrations, an approach well known from the development of drugs like taxol or methothrexate. In addition, for many of the newer small-molecule drugs, attacking single or multiple targets of protein kinase networks off-target toxicity is likely to occur. The increased efficacy, however, might offset the burden of toxicity to some extent.

The high complexity of cancer as a disease and the issues related to the design of clinical trials in oncology contribute to the low success rate in this therapeutic area. In the design phase of clinical trials, the definition of study endpoints (primary outcome measures) and the selection of patient eligibility criteria are amongst the most difficult steps. The classical endpoints for drug approval have been survival, time to progression (TTP), or progression-free survival (PFS). There are, however, problems with each of them. Even the endpoint of survival, seen as the "gold standard" in oncology trials, has been potentially confounded by the administration of efficient second or further lines of therapy. TTP and PFS have the advantage of not being confounded by various lines of therapy; however, progression is sometimes difficult to measure, assessments (CT scans or MRI) tend to occur as scheduled observations, and results are more related to protocol design than clinical reality. Tumor response rates as surrogates for a clinical benefit, although assessing the objective shrinkage of the tumor, are equally dependent upon the frequency of evaluations and can potentially be misleading in cases of asymptomatic progression. The definition of the primary outcome and related monitoring schedule will have a significant impact on overall outcome of the clinical development effort. There are many trials of new compounds that have failed to demonstrate a clinical benefit when compared to standards of care. The exceptional heterogeneity and variability in tumor response has resulted in the attempt to categorize patient populations by applying selection criteria based on biomarkers characteristic to the target and mechanism of action. Several novel designs have been tested, such as "enrichment designs" in two-stage Phase II studies, and "randomized discontinuation" design, all aiming to increase the predictive value of early clinical development. So far, major improvements in success rates of anticancer drug development have not been reported. High attrition rates as well as low response rates to new treatments remain rather common.

Summary

Comparing the number of approvals of new chemical entities and biologics by the FDA and the European regulatory authorities throughout the past couple of years to the growing cost of development, there continues to be a gap in productivity, despite advances in the improvement of clinical trial design and effectiveness. And the industry continues to generally believe that this productivity gap can be overcome by investing further in both traditional research and development.

The major differences among the three major therapeutic areas discussed need to be better understood, including the inherent complexity of the disease under investigation, the underlying pathophysiological and pharmacogenetic mechanisms, and the mechanisms of drug activity. Major roadblocks still need to be overcome, including the identification and validation of biomarkers to assess safety and efficacy both in animal models and in humans in order to improve the success rate of drug development, bringing new safe and efficacious drugs to the market more quickly. ◆

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Dr. Udo Kiessling is Corporate Vice President and Worldwide Head of Medical Affairs, Clinical Research Services at PAREXEL. Dr. Kiessling advises clients and provides strategic support in their clinical development planning, including in the presentation of safety and efficacy data to Data Safety Monitoring Boards for complex, multinational clinical studies. He oversees a global staff of experts with a broad range of therapeutic experience, who provide medical affairs and medical writing expertise. Dr. Kiessling has more than 16 years of experience in clinical research. Prior to joining PAREXEL, he was Vice President of Clinical Research and Business Development at the German-American Institute for Biomedical Research GmbH. Previously, he served as Head of Clinical Research at Schering-Plough in Germany, where he led clinical studies in the areas of oncology and infectious diseases and was Head of the Virology Department at the Center for Molecular Biology and Medicine in Berlin. Dr. Kiessling earned his PhD in Virology/Molecular Biology from Moscow State University and completed his Doctorate in Medicine at the Medical School of Hanover, Germany, where he continues to be member of the faculty. He has authored numerous papers on the topics of tumor virology and molecular biology and holds several patents in the biotechnology area.

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SARs Analysis

By: John A. Bermingham

This is not an article about Severe Acute Respiratory Syndrome. It is about the importance of achieving tangible or intangible results that are quantified or perceived. First, what is a SARs Analysis? In this column, SARs stands for Situation, Action, and Results. The SARs Analysis is set up as a spread sheet with three columns. The first is the Situation column in which you write down what the situation that you are facing. The second is the Action column in which you write down what actions you are taking to resolve the situation. And the third is the Results column in which you write down the results of the actions that you took.

So the other day, our Executive Director, Dan Marino, and I were communicating via e-mail, and he posed an idea for this article. "What about a leader who only SPEAKS about great things and only points out problems (no solutions offered) compared to a leader who actually DOES great things and provides solutions to problems," he suugested. Great question. Great topic.

The two most important things that denote great leadership are the ability to provide leadership and to drive results. Leaders cannot get by with "I tried" or "I hoped that" or something similar. Leadership success is measured by great results.

There are many people in both the private and public sectors who are great orators. I believe this is one of the marks of a great leader. The ability to communicate effectively and motivate people is a great and necessary talent for leaders. Great leaders communicate the situation and get their people motivated and committed to resolving the issues. So what if that's the end of the story?

Well, I would say that the "motivated troops" are nothing more than that. Just motivated. What about the action plans? Whose job is it to formulate those? What are the expected results? This is where the great leaders and the "empty suits" separate from each other. The "empty suit" goes no further than to opine on the situation, point out the problems, and then leaves it at that. When nothing happens to resolve that situation, ie, no action plans and anticipated measurable results developed, then there is a failure of leadership.

Great leaders, after recognizing a situation that needs to be addressed and resolved, or having it brought to him/her by others, immediately assess the situation and then, along with the necessary people, develop the action plans and anticipated results and then provide the leadership to drive to the intended results.

What I find interesting today is that too many CEOs or leaders don't go much further than to assess the situation. After that, nothing. This is pontification, not leadership. I also find it interesting that today's Presidential candidates are excellent at opining on healthcare reform, the economy, Iraq, illegal immigrants, terrorists, etc. What I would really like to hear is a SARs analysis on the key issues facing our country by these candidates.

One other thought. The next time you are going to your boss' office for a performance review, to ask for a raise, or to discuss why you should be considered for a promotion, develop a written SARs analysis on your past performance. You will probably end up with 5 or 10 situations in which you developed actions plans for and what the results were. This is very solid evidence on your accomplishments and is very powerful ammunition to prove your value-add and capability to drive results. It will also reflect well on your boss with his/her management! ◆

Biography

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

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