Drug Delivery® Technology

January 2008 Vol 8 No 1 www.drugdeliverytech.com

What Are Hydrocapsules?

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

Mr. Stephen From
Advancing Delivery of Ophthalmic Therapeutics Through Iontophoresis

Mr. Ara Manukian
Hydrocapsules®: A New Method for Aqueous Drug Delivery

Raj Khankari, PhD, MBA
CIMA: More Than Orally Disintegrating Tablets

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MR. GEOFF BENNETT

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SPECIALTY PHARMA
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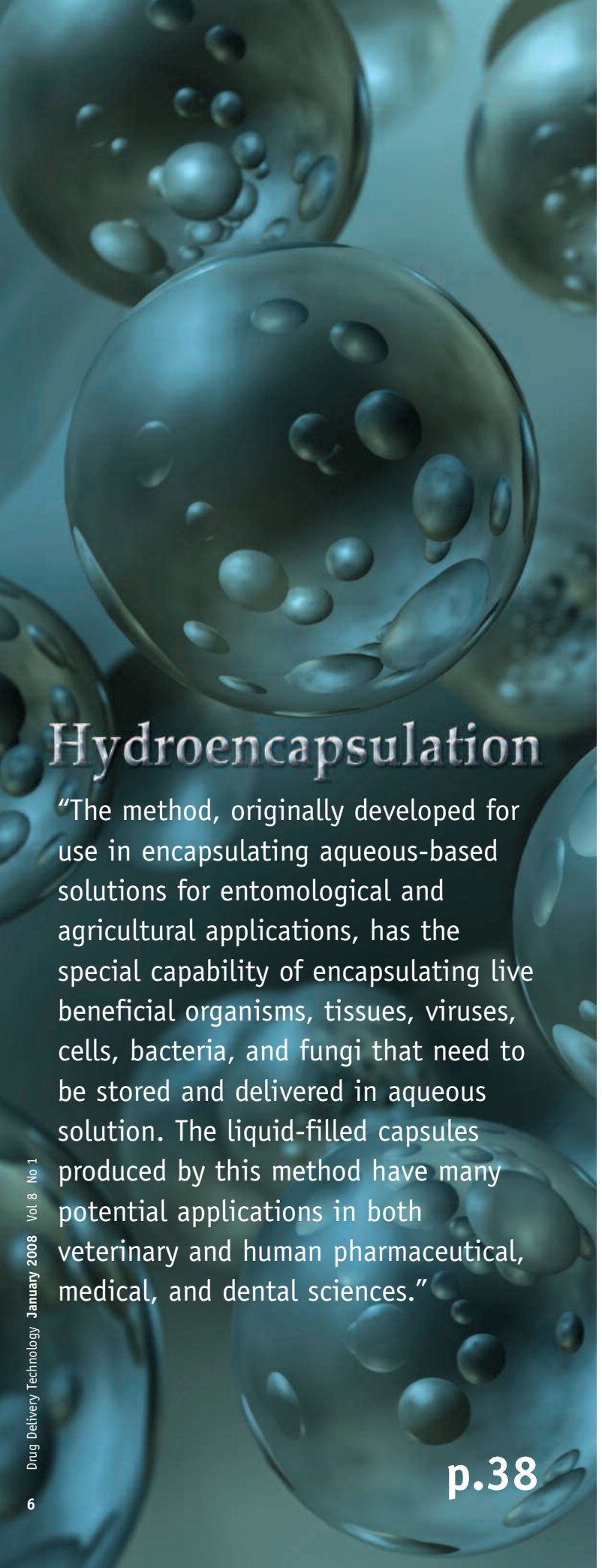

Hydroencapsulation

"The method, originally developed for use in encapsulating aqueous-based solutions for entomological and agricultural applications, has the special capability of encapsulating live beneficial organisms, tissues, viruses, cells, bacteria, and fungi that need to be stored and delivered in aqueous solution. The liquid-filled capsules produced by this method have many potential applications in both veterinary and human pharmaceutical, medical, and dental sciences."

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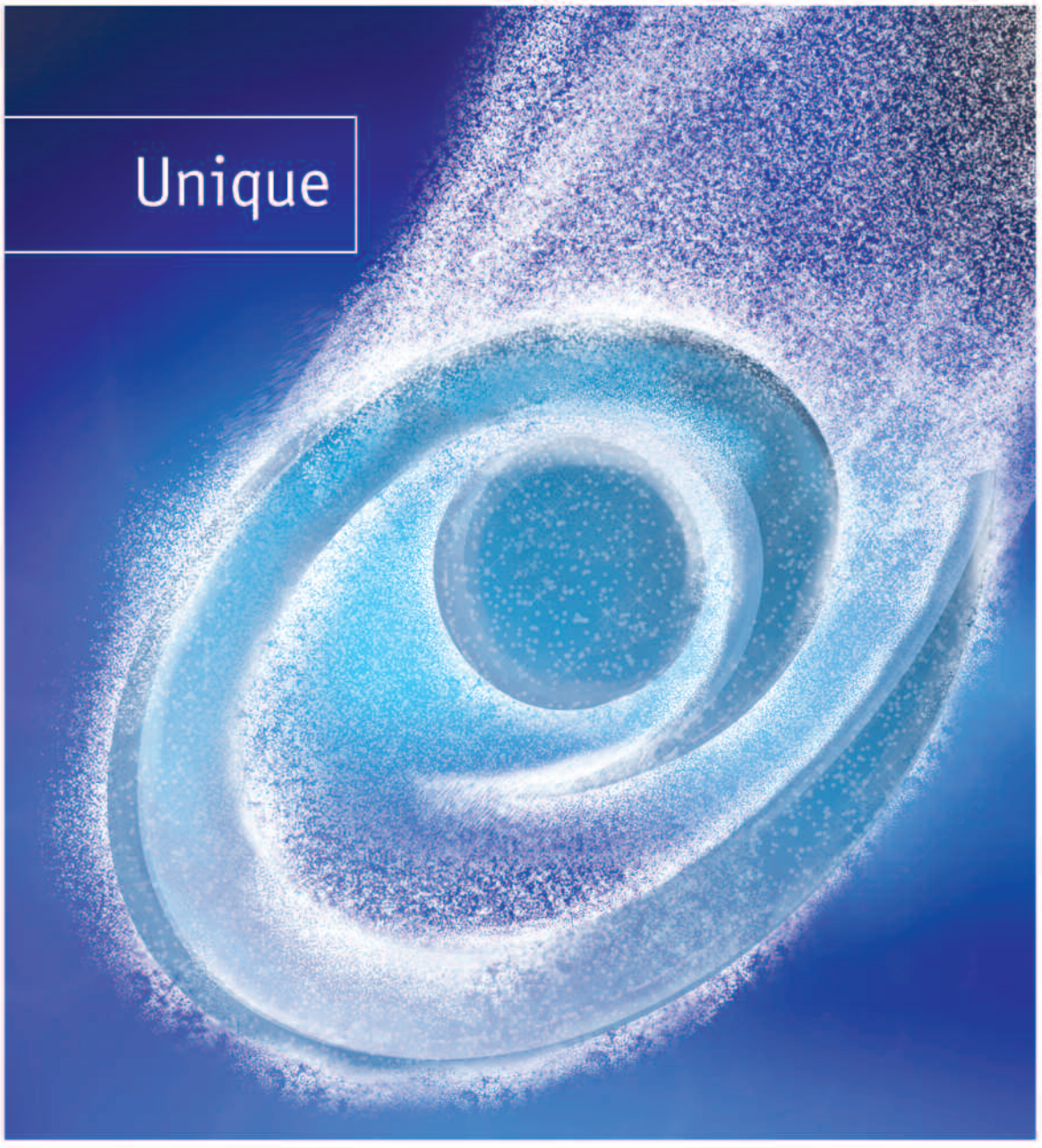

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ODT CUSTOMIZED RELEASE TASTE MASKING ENHANCED BIOAVAILABILITY

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Focus on the Eye

"In order to effectively deliver ophthalmic drugs iontophoretically, a technology should be able to deliver a range of therapeutics to both the anterior and posterior tissues of the eye, and the drugs must initially be adapted for iontophoretic delivery. EyeGate has concentrated its efforts on optimizing the EyeGate II Delivery System and developing a highly specialized laboratory dedicated to formulating drugs for this delivery method."

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Departments

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Market News and Trends

Genzyme Corporation Study of Myozyme for Late-Onset Pompe Patients Meets Co-Primary Efficacy Endpoints

Genzyme Corp. recently announced its Late Onset Treatment Study (LOTS) of Myozyme (alglucosidase alfa) met its co-primary efficacy endpoints. The study was undertaken to evaluate the safety and efficacy of Myozyme in juvenile and adult patients with Pompe disease. Myozyme was first approved in 2006, and the product is now registered in 36 countries.

The randomized, double-blind, placebo-controlled study enrolled 90 patients at eight primary sites in the United States and Europe. Participants received Myozyme or a placebo every other week for 18 months. The average age of study participants was 44 years. The primary efficacy endpoints of the study sought to determine the effect of Myozyme on functional endurance as measured by the 6-minute walk test and to determine the effect of Myozyme on pulmonary function as measured by percent predicted forced vital capacity. The results showed that, at 18 months, patients treated with Myozyme increased their distance walked in 6 minutes by an average of approximately 30 meters compared with the placebo group (P = 0.0283; Wilcoxon test). The placebo group did not show any improvement from baseline. The average baseline distance walked in 6 minutes in both groups was approximately 325 meters. Percent predicted forced vital capacity in the group of patients treated with Myozyme increased by 1% at 18 months. In contrast, it declined by approximately 3% in the placebo group (P = 0.0026; Wilcoxon test). The average baseline percent predicted forced vital capacity in both groups was approximately 53%. The results for both efficacy endpoints were consistent across various prospectively defined subgroups.

The safety of Myozyme was similar to placebo in the LOTS study. The number of patients with serious and treatment-emergent non-serious adverse events was similar in the Myozyme and placebo groups. Approximately 25% of patients in each group experienced infusion-associated reactions. There was one death in the Myozyme group unrelated to treatment. Genzyme is completing an analysis of the study results and will apply in the second half of next year for potential inclusion of the results in the product labeling. Detailed results will be presented at medical congresses throughout the world by the study investigators and submitted for publication in a peer-reviewed journal. Myozyme used in the LOTS study was produced at Genzyme's Allston Landing facility using the larger scale manufacturing process (2000 L) that is currently approved by 35 countries. The FDA is currently reviewing Genzyme's application for approval of this larger scale process.

One of the world's leading biotechnology companies, Genzyme is dedicated to making a major positive impact on the lives of people with serious diseases.

Elan Responds to Biogen Idec's Decision to Stay Independent

The Board of Directors of Biogen Idec Inc. recently announced that, after completing a review of strategic alternatives to maximize shareholder value, Biogen Idec will continue on its present course as an independent company. This past October, the Board announced the start of a process to determine whether potential strategic interest on the part of major pharmaceutical companies might result in superior value for stockholders in the current environment. Biogen Idec, which was represented by independent financial advisors Goldman Sachs & Co. and Merrill Lynch & Co., conducted a comprehensive and thorough sale process. At the conclusion of this process, Biogen Idec did not receive any definitive offers to purchase the company. The Board emphasized that Biogen Idec's business strategy is working and generating strong operating and financial performance. The Board noted that it is confident that continued execution of the company's business plan will result in attractive value for stockholders.

In response to Biogen Idec Inc.'s recent announcement that it has completed its strategic review and will continue its present course as an independent company, Elan Corporation, plc recently reaffirmed its commitment to Tysabri and the patients who are and will benefit from this treatment. Specifically, Elan intends to continue to work effectively with Biogen Idec on securing FDA approval of the pending CD indication and realizing the full potential of Tysabri in the Multiple Sclerosis marketplace.

Although Elan was not privy to the strategic evaluation process conducted by Biogen Idec since its October 12, 2007, announcement, Elan previously indicated its receptivity to the possible restructuring of its existing Collaboration Agreement in connection with a third party's acquisition of Biogen Idec.

Elan Corporation, plc is a neuroscience-based biotechnology company committed to making a difference in the lives of patients and their families by dedicating itself to bringing innovations in science to fill significant unmet medical needs that continue to exist around the world. Elan shares trade on the New York, London, and Dublin Stock Exchanges.

Biogen Idec, formed in November 2003 from the merger of Biogen, Inc. and IDEC Pharmaceuticals Corporation, creates new standards of care in oncology and immunology. As a global leader in the development, manufacturing, and commercialization of novel therapies, Biogen Idec transforms scientific discoveries into advances in human healthcare.

Two blockbuster drugs lead Biogen Idec's product line-up, each with current annual net sales of more than $1 billion. The first is Rituxan (rituximab), which was discovered by IDEC, for the treatment of certain B-cell non-Hodgkin's lymphomas (NHL), which Biogen Idec co-promotes in the United States with Genentech, and Avonex (Interferon beta-1a), which is indicated for the treatment of patients with relapsing forms of multiple sclerosis

The company has a pipeline of 10 products in clinical development. Two of these products are in Phase III clinical trials: Rituxan, in partnership with Genentech and F. Hoffman-LaRoche, for the treatment of rheumatoid arthritis and other cancer indications, and Antegren (natalizumab), in partnership with Elan Corporation plc, for the treatment of MS and Crohn's disease. Biogen Idec is headquartered in Cambridge, MA, and maintains centers of excellence in San Diego, California, and Cambridge focused on oncology and immunology. The company has additional offices in Canada, Australia, Japan, and throughout Europe.

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Market News and Trends

Transport's Phase II Data Show Single Treatment SoloVir ETS Significantly Stops Progression of Cold Sore Episode

This past November at the 19th Annual Piper Jaffray Health Care Conference, Dr. Dennis I. Goldberg, President and CEO of Transport Pharmaceuticals, Inc., presented compelling clinical results of a Phase II study designed to evaluate the safety and efficacy of the company's lead drug/device product, the SoloVir Electrokinetic Transdermal System (SoloVir ETS) for recurrent herpes labialis (cold sores). SoloVir ETS uses single-use drug cartridges containing Transport's novel, 5% acyclovir gel.

This unique study was designed to determine the optimum treatment protocol based upon the immediate delivery of a large bolus of acyclovir into the skin during a herpetic episode, ie, whether treatment at either the prodrome or erythema stage on day 1 of the herpetic episode was significantly better than placebo. TPI-H-221 was a multi-center, randomized, double blind, placebo-controlled study that enrolled approximately 260 subjects.

Dennis I. Goldberg, President and CEO, said "The TPI-H-221 study has demonstrated that treatment at the erythema or papule/edema stages, the first visible signs of a cold sore, decreased the number of patients who progressed to classical lesions, and resulted in a significant decrease in healing times. Patients who were treated earlier, at the prodrome stage, did not see a statistically significance benefit. Our Phase II study provides valuable insights into the treatment of herpes labialis. SoloVir ETS is the only one-time treatment to achieve a statistically significant and clinically meaningful decrease in herpetic lesions. This study provides a number of important findings that provide a clear path for completing the development of this novel combination drug/device product."

Spotswood Spruance, MD, a noted expert on herpes labialis and a member of Transport's Scientific Advisory Board, added "Based on two well-controlled Phase II clinical studies, Transport may offer the clinical community a new paradigm for treating herpes more efficaciously by administering treatment to the site of viral replication at the first visible evidence of a lesion."

Dr. Spruance continued "There has been some controversy in the medical community about treating this patient population during the prodrome stage because as many as one third will have aborted lesions without receiving any treatment. SoloVir ETS may mitigate that controversy by allowing patients to wait for the first visual signs before initiating treatment, thereby treating patients with a higher probability of progression to classical lesion."

Data from this Phase II clinical study indicate that treatment at the erythema or papule/edema stages resulted in a statistically significant effect on the herpetic episode. In particular, the study demonstrated a 79% increase in aborted lesions (43% active; 24% placebo; $p = 0.03$; active $n = 61$; placebo $n = 72$) in SoloVir ETS-treated subjects versus placebo. These subjects also experienced a 3.5-day reduction in time to complete healing ($p = 0.015$). Furthermore, this study demonstrated a statistically significant and clinically meaningful reduction in pain. SoloVir ETS was shown to be well tolerated with a compliance rate greater than 98%, with no serious adverse events reported related to study drug in all groups.

Based on the strong clinical results from TPI-H-221, Transport will advance SoloVir ETS into its next clinical stage of development in 2008. Transport has retained worldwide rights to SoloVir ETS for the treatment of herpes labialis.

Transport is bringing together cutting-edge medical electronics with drug formulation and material sciences to develop drug/device combination products that enhance movement of drugs across the stratum corneum (the skin's outer layer) by means of electric current. In addition to the lead drug/device product, SoloVir ETS, Transport has a pipeline of earlier stage dermatological products based on its electrokinesis platform, including onychomycosis, acne, actinic keratosis, keloids, warts, psoriasis, skin cancer, and medical aesthetic applications.

FMC Corporation & Pronova BioPharma Announce Agreement to Develop New Alginate-Based Capsule Products

FMC Corporation and Pronova BioPharma ASA recently announced the companies have entered into a worldwide license and development agreement to develop products using a novel capsule technology developed by FMC. The alginate-based capsule technology is expected to significantly strengthen the product life-cycle management of Pronova BioPharma's products and has the potential for use both with Pronova BioPharma's current active pharmaceutical ingredient, marketed as Omacor in Europe and Lovaza in the US, as well as in future products under development. Under the terms of the agreement, FMC will apply its technology to Pronova BioPharma's products while Pronova BioPharma will be responsible for the clinical development and for securing regulatory approval. Pronova BioPharma plans to initiate clinical trials in early 2009 and launch of the new capsule is expected in 2010-2011.

FMC's novel proprietary capsule technology uses alginate, a marine plant-derived biopolymer, as the main component in the capsule shell. Alginate is gastro-resistant, providing an enteric release profile that delays release of the drug until passage from the stomach into the intestine. The technology also has the benefit of producing a seamless capsule with a significantly thinner shell wall, reducing the size of the capsule by approximately 25%. The enteric release profile and smaller capsule size are expected to result in increased patient compliance.

"The new alginate capsule technology has the potential to deliver significant benefits for patients, as well as creating important patent life-extensions for Omacor/Lovaza and other products under development in our pipeline," said Tomas Settevik, CEO of Pronova BioPharma. "We look forward to working with FMC in bringing the new capsule technology to market, which we anticipate taking place by 2010-2011."

"We are delighted to partner with Pronova BioPharma to combine our leading-edge oral dose technology with such an important pharmaceutical product franchise," added Ted Butz, Vice President and General Manager, FMC Specialty Chemicals Group

FMC Corporation is a diversified chemical company serving agricultural, industrial, and consumer markets globally for more than a century with innovative solutions, applications, and quality products. The company operates its businesses in three segments: Agricultural Products, Specialty Chemicals, and Industrial Chemicals.

FMC BioPolymer, a division of FMC Specialty Chemicals Group, is the world's leading producer of alginate, carrageenan, and microcrystalline cellulose.

Pronova BioPharma is a global leader in the research, development, and manufacture of marine-originated, omega-3 derived, pharmaceutical products. Pronova BioPharma's first commercialized product is branded as Omacor in a number of countries throughout Europe and Asia and as Lovaza in the US. The product is manufactured at Pronova BioPharma's plant in Sandefjord, Norway, using a unique and complex process.

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Market News and Trends

Acura Pharmaceuticals Announces Receipt of $30-Million Cash Payment & Closing of Agreement With King Pharmaceuticals

Acura Pharmaceuticals, Inc. recently announced the closing of the license, development, and commercialization agreement with King Pharmaceuticals Research and Development, Inc., a subsidiary of King Pharmaceuticals, Inc. and receipt of the initial $30-million non-refundable cash payment from King under the agreement. The agreement closing was subject to clearance under the Hart-Scott-Rodino Antitrust Improvements Act, which was received December 6, 2007. Upon the closing of the agreement, the company paid off its $5-million secured term note in accordance with the agreement and the prepayment provisions of the secured term note. The company now has no term debt on its balance sheet.

The agreement provides King with an exclusive license in the United States, Canada, and Mexico for Acurox Tablets plus another undisclosed opioid product candidate utilizing Acura's Aversion Technology. In addition, the agreement provides King with an option to license in the territory all future opioid analgesic products developed utilizing Acura's Aversion Technology. In addition to the $30-million initial payment, Acura could also receive additional cash payments from King of up to $28 million for Acurox Tablets and similar amounts with respect to each future product licensed based on successful achievement of certain development and regulatory milestones specified in the agreement.

King will reimburse Acura for all Acurox Tablet research and development expenses incurred beginning from September 19, 2007, and all research and development expenses related to future products after King's exercise of its option to an exclusive license for each future product. King will record net sales of all products and pay Acura a royalty ranging from 5% to 25% based on the level of combined annual net sales for all products subject to the agreement. King will also make a one-time cash payment to Acura of $50 million in the first year in which the combined annual net sales of all licensed products exceed $750 million.

Acura Pharmaceuticals, Inc. is a specialty pharmaceutical company engaged in research, development, and manufacture of innovative Aversion (abuse deterrent) Technology and related product candidates.

Endo & Penwest Receive New Paragraph IV Certification Notice From IMPAX for Opana ER

Pharmaceuticals Holdings Inc. and Penwest Pharmaceuticals Co. recently announced they received a notice from IMPAX Laboratories, Inc. advising of the FDA's acceptance for substantive review, as of November 23, 2007, of IMPAX's Abbreviated New Drug Application (ANDA) containing a new Paragraph IV certification under 21 U.S.C. § 355(j) for oxymorphone hydrochloride extended-release tablets CII. IMPAX stated in its letter that the FDA requested IMPAX to provide notification to Endo and Penwest of this certification. This Paragraph IV certification notice refers to Penwest's US Patent Nos. 7,276,250, 5,958,456 and 5,662,933, which cover the formulation of Opana ER. These patents are listed in the FDA's Orange Book and expire in 2022, 2013, and 2013, respectively. In addition to these patents, Opana ER has a new dosage form (NDA) exclusivity that prevents final approval of any ANDA by the FDA until the exclusivity expires on June 22, 2009.

Endo and Penwest are currently reviewing the details of this new notice from IMPAX and will continue to pursue all available legal and regulatory avenues in defense of Opana ER, including enforcement of their intellectual property rights and approved labeling.

Endo Pharmaceuticals Holdings Inc. is a fully integrated specialty pharmaceutical company with market leadership in pain management products. Through its Endo Pharmaceuticals Inc. subsidiary, the company researches, develops, produces, and markets a broad product offering of both branded and generic pharmaceuticals, meeting the needs of healthcare professionals and consumers alike.

Penwest is a drug development company dedicated to bringing to the marketplace innovative products that help improve the lives of patients. The company's goal is to identify, develop, and commercialize prescription products that address unmet medical needs, primarily for diseases of the nervous system. Penwest is currently applying its drug delivery and drug development expertise to a pipeline of potential products that are in various stages of development and that it intends to commercialize independently or through third-party alliances.

Merck KGaA & Idera Pharmaceuticals to Collaborate on Development of TLR9 Agonists for Cancer

Merck KGaA recently announced it has entered into a worldwide licensing and collaboration agreement on behalf of its Merck Serono division with Idera Pharmaceuticals, Inc. of Cambridge, MA, for the research, development, and commercialization of Idera's Tolllike Receptor 9 (TLR9) agonists for the treatment of cancer. Under the agreement, Idera has agreed to exclusively license the therapeutic oncology applications, excluding their use with cancer vaccines, of its lead TLR9 agonists, IMO-2055 and IMO-2125. In addition, Merck and Idera have agreed to engage in a research collaboration to identify a specified number of novel, follow-on TLR9 agonists, which will be derived using Idera's chemistry-based approach and for which Merck will have the exclusive right to use in oncology applications other than cancer vaccines.

"Merck is committed to the development of innovative approaches to cancer therapies on a global basis, and we expect that this collaboration with Idera will help us move toward that goal," said Vincent Aurentz, Executive Board Member and Head of Portfolio Management and Business Development for the Merck Serono division. "We believe TLR9 agonists represent a novel mechanism of action with great potential and we look forward to advancing their development for various oncology indications."

Under the terms of the agreement, Merck has agreed to pay an up-front license fee of $40 million to Idera. In addition, Idera is eligible to receive milestone payments of up to $381 million based on current exchange rates, depending on success in achieving clinical development and commercialization, as well as royalties on sales of any products developed and commercialized by Merck based on IMO-2055, IMO-2125, or the follow-on TLR9 agonists. The contract will take effect, and the up-front fee will be paid following regulatory clearance under the Hart-Scott-Rodino Antitrust Improvements Act.

"Idera has chosen to collaborate with Merck KGaA for the application of our TLR9 agonists in oncology because of its proven capabilities and success in developing novel therapies for cancer and its commitment to global research, development, and commercialization in this area," said Sudhir Agrawal, Chief Executive Officer and Chief Scientific Officer of Idera.

Idera Pharmaceuticals is a drug discovery and development company that is developing drug candidates to treat cancer and infectious, respiratory, and autoimmune diseases, and for use as vaccine adjuvants. Idera's proprietary drug candidates are designed to modulate specific TLRs, which are a family of immune system receptors. Idera's pioneering DNA chemistry expertise enables it to identify drug candidates for internal development and creates opportunities for multiple collaborative alliances.

Market News and Trends

Bristol-Myers Squibb Company & Gilead Sciences Expand Alliance

Bristol-Myers Squibb Company and Gilead Sciences, Inc. recently announced an agreement to commercialize Atripla (efavirenz 600 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg) in Europe for the treatment of virologically suppressed adults with HIV-1 infection, subject to the product's approval by the European Commission. If approved, Atripla would represent the first and only once-daily single-tablet regimen for HIV-1 infection in the European Union. The companies expect the European Commission to issue its decision by the end of the year.

Under this agreement, Bristol-Myers Squibb and Gilead share responsibility for commercializing Atripla throughout the European Union and certain other European countries. Gilead will record revenues from future net sales of Atripla in most of the European countries, while Bristol-Myers Squibb will record revenues in most of the European countries at percentages relative to the contribution represented by its individual product.

Bristol-Myers Squibb recently concluded an agreement with Merck & Co., Inc. under which Merck granted Bristol-Myers Squibb rights to co-commercialize Atripla with Gilead in all of the European Union and certain other European countries. Previously, Merck had the exclusive right to market any product containing efavirenz (a component of Atripla) in all European countries other than the United Kingdom, Germany, France, Italy, Spain, and the Republic of Ireland.

Efavirenz is marketed by Bristol-Myers Squibb under the tradename Sustiva in the United States, Canada, and six major countries of the European Union. Efavirenz will continue to be commercialized by Merck & Co, Inc, through its affiliate Merck Sharp & Dohme (MSD) Limited under the tradename Stocrin in all other countries within the European Union and many countries outside of the United States. Emtricitabine and tenofovir disoproxil fumarate are commercialized by Gilead under the tradenames Emtriva and Viread, respectively, and are commonly prescribed together as a once-daily, fixed-dose tablet marketed under the tradename Truvada for use as part of combination therapy.

Atripla is currently sold in the United States and Canada through a joint venture between Bristol-Myers Squibb and Gilead. Atripla was approved by the US Food and Drug Administration in July 2006 and by Health Canada in October 2007. Gilead and Merck previously announced a collaboration to distribute Atripla in developing countries.

Gilead Sciences is a biopharmaceutical company that discovers, develops, and commercializes innovative therapeutics in areas of unmet medical need. The company's mission is to advance the care of patients suffering from life-threatening diseases worldwide. Headquartered in Foster City, California, Gilead has operations in North America, Europe, and Australia.

Geron Corporation Receives Milestone Payment From Merck for Telomerase Cancer Vaccine Candidate

Geron Corporation recently announced that Merck & Co, Inc. has filed an Investigational New Drug application with the US FDA for a cancer vaccine candidate that targets telomerase. Merck is developing the vaccine under a July 2005 Research, Development, and Commercialization License Agreement with Geron, which provided Merck with exclusive worldwide rights to develop and commercialize non-dendritic cell-based vaccines targeting telomerase. Geron has received a $4-million milestone payment from Merck on account of the IND filing, and is eligible to receive additional development milestones as well as royalties on worldwide product sales.

"We are pleased with the progress that Merck has made in advancing this program toward the clinic," said Thomas B. Okarma, PhD, MD, Geron's President and CEO. "We appreciate the collaborative nature of our relationship with Merck and look forward to working with them to realize the therapeutic potential of this cancer vaccine candidate."

Separately, Geron is currently enrolling patients with acute myelogenous leukemia (AML) in a Phase I/II study of its own telomerase vaccine candidate, GRNVAC1, which delivers the telomerase antigen using autologous dendritic cells. In a prior study conducted at Duke University, the vaccine was shown to induce substantial T-cell anti-telomerase activity. The Geron study also incorporates a prime/boost vaccine dosing regimen designed to prolong the period of anti-telomerase immunity. Geron is also developing a second-generation allogeneic telomerase vaccine based on dendritic cells made from human embryonic stem cells.

Telomerase is an enzyme, active in most cancer cells, that maintains telomere length at the ends of chromosomes. This activity confers replicative immortality to the cells in the tumor, allowing the cancer to grow and metastasize over long periods of time. Because telomerase is inactive or only transiently expressed in normal human tissues, and is critical to the growth and progression of most cancer types, it is regarded as a universal and specific cancer target.

Geron is developing first-in-class biopharmaceuticals for the treatment of cancer and chronic degenerative diseases, including spinal cord injury, heart failure, and diabetes. The company is advancing an anti-cancer drug and a cancer vaccine that target the enzyme telomerase through multiple clinical trials. Geron is also a world leader in the development of human embryonic stem cell-based therapeutics, with its spinal cord injury treatment anticipated to be the first product to enter clinical development.

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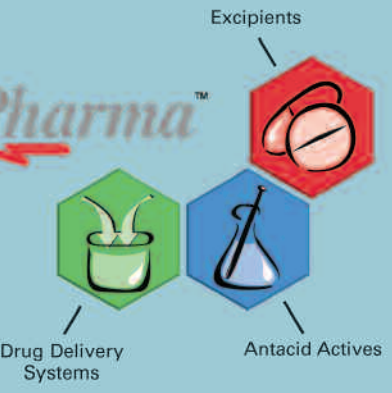

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BUSINESS DEVELOPMENT

An Inside View of a 2007 Drug Delivery Deal: SurModics & Brookwood

By: Dan Marino, MSc, Executive Director, Drug Delivery Technology

Solid drug delivery acquisitions, such as the Brookwood transaction, cause a great deal of excitement in the industry. Drug delivery leaders are interested to learn how the strategy for acquisition came about and how it was successfully achieved. We asked Arthur J. Tipton, PhD, President of Brookwood Pharmaceuticals, and Bruce Barclay, CEO and President of SurModics, to communicate their thoughts leading up to the deal, their insights on the successful execution, and their plans for the future as an integrated company.

BACKGROUND

SurModics, Inc., a leading provider of surface modification and drug delivery technologies to the healthcare industry, announced this past August that it had acquired Brookwood Pharmaceuticals, Inc., a leading provider of drug delivery technology primarily to the pharmaceutical industry, from Southern Research Institute (SRI). SurModics paid $40 million in cash at closing and may pay up to an additional $22 million in cash upon the successful achievement of certain revenue targets and development, regulatory, and other milestones associated with customer projects. Brookwood generated $12.7 million of revenue and strong year-over-year growth in calendar year 2006, with the majority coming from research and development fees. Furthermore, Brookwood is profitable and cash flow positive. The acquisition is expected to be neutral to modestly accretive to SurModics' fiscal 2008 earnings and significantly accretive thereafter. Goldman, Sachs & Co. served as financial advisor to SurModics in this transaction, and Brookwood and its shareholder, Southern Research Institute, were represented by Stonecroft Capital, LLC.

Let's go back to the beginning. How did the Brookwood spin-out from SRI come about? Why did you believe it was a good opportunity for SRI?

ART: As part of the not-for-profit SRI, the prime focus of that group over a 30-year history was as a technology center of excellence for controlled release and medical applications of biodegradable polymers. This group played an integral role in many technologies and products, including the first commercial microsphere drug products in Europe and the US, as well as the Atrigel technology of Atrix (now QLT). More recently, this group had in parallel developed its own proprietary technologies and manufacturing capabilities, and with these accomplishments, was poised to become a profitable, stand-alone venture. The other key item was the timing and viability of staff. There were a number of senior people who had worked together previously that were available and excited about joining forces in a new start-up.

Is there anything associated with the original spin-off and start-up of Brookwood that you would have done differently?

ART: No. We really had an excellent start. There was great support from Southern Research, our employees, the local community, and our clients. We also launched at a very good time in the industry and were successful in our first year of attracting new customers.

Were there any legacy issues that made it challenging to get the SurModics deal accomplished?

ART: I would not say there were any issues that made closing the deal challenging; perhaps some that made it like every other deal in that there were some unique aspects. For example, when we launched Brookwood, we did so by spinning a group out of Southern Research. We formed a Board of Directors as a standard incorporation step. As we only had one stockholder in Southern Research, in a sense the shareholders' meeting took place at the Board level at Southern Research. So in this deal, the approvals took place in two separate board meetings.

Also, when launching out of a not-for-profit, we were able to create new incentive metrics. For example, Southern Research had an incentive program that primarily rewarded only inventors on patents. As we formed Brookwood, we were able to create an incentive program in the form of stock options that provided incentives to all employees and bound us together to jointly achieve common goals.

Did your team and SRI have a predetermined timeframe for a liquidity event of the magnitude of the strategic merger with SurModics at the time of spin-out?

ART: We did not have timing objectives for a liquidity event. In effect, the only stakeholders were Southern Research and the Brookwood employees, both of whom were patient in building value. Quite simply, the team at SurModics

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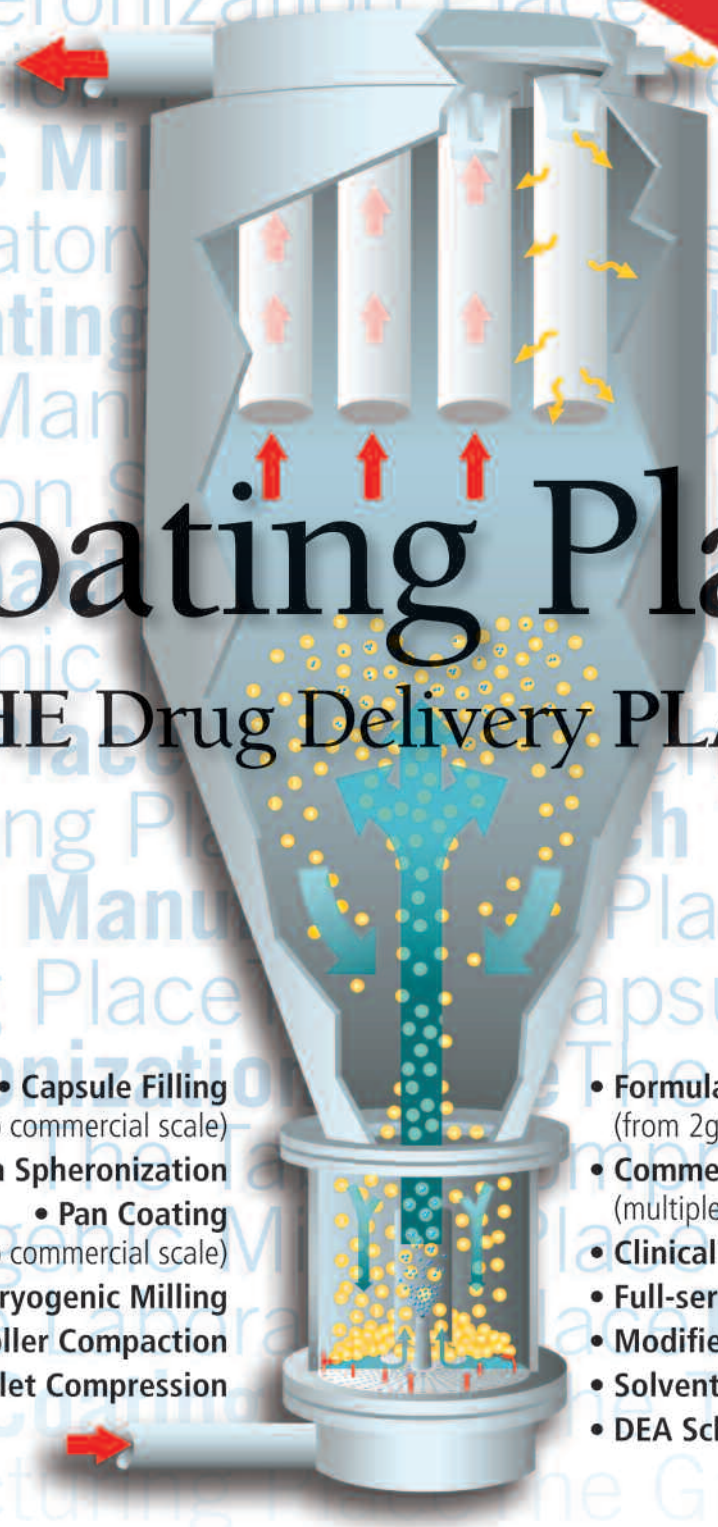

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convinced us that we could enhance all of our business goals via the acquisition, that we would be able to deliver even more value for our clients with expanded capabilities.

Why do you believe the timing of this acquisition was right?

ART: Brookwood had begun a process that was targeted to lead to an equity investment. We were looking for additional capital, primarily to drive a number of growth opportunities, most notably to add manufacturing capacity to continue to support our customers' products.

How did the Brookwood opportunity present itself, and why was the company targeted as an acquisition?

BRUCE: We had targeted systemic drug delivery as an area of interest through our strategic planning process. As such, we developed an initial list of companies in the systemic drug delivery field we believed would complement our core competencies and strengthen our polymer-based drug delivery franchise. Brookwood stood out on this list, so we were happy to set an initial meeting with them in our offices in September 2006, more than 10 months prior to announcing the acquisition.

How were the merger discussions initiated?

BRUCE: Following a preliminary meeting in September 2006 and a series of face-to-face meetings in the first 3 months of 2007, both groups moved quickly to substantial discussions. One of the most productive communications was weekly phone calls between me and Art. We executed a term sheet at the end of April and then entered the substantial diligence in the May-July time point.

Can you describe the strategic fit between Brookwood and SurModics?

BRUCE: The way I have described the transaction is that it was driven by both synergy and diversity. Synergy in that both groups are dedicated to drug delivery and in particular to polymer-based drug delivery. Both groups have also realized the value of customer service and strong collaborative relationships. The diversity comes from the fact that we have different technologies and to a substantial level, we have targeted different markets: SurModics the medical device industry and Brookwood the pharma and biotech.

Did you realize the strength of the fit at the time SurModics first approached you?

ART: The synergy and positives of a combined entity became apparent fairly early in the process of getting to know each other. Both companies with a clear focus and commitment to drug delivery, but with diversified technologies and market focus. As we continued the process of diligence, we realized there was compatibility in our business models, customer service, and growth plans. In one example, both groups focus intensely on increasing intellectual property on an ongoing basis.

Did you fully understand the strength of the Brookwood opportunity for SurModics?

ART: It is an interesting question. We had more than tripled revenue and programs in less than 3 years, accompanied by expanding technologies and capabilities. For example, we added aseptic clinical trial manufacturing capacity to enable clients with products, such as peptides and proteins to advance to the clinic. We accomplished this growth by strong marketing efforts and technology expansion, so it was not as if we had one seminal event, but rather consistent advancement. When you take a break and look back, you realize that the staff has built and achieved something of tremendous value.

As CEO, what steps did you take when you received the first serious overtures from SurModics?

ART: I immediately informed the Brookwood Board of Directors, who subsequently authorized me to proceed with preliminary discussions. The President of Southern Research was Chair of that Board, and with him, we next informed the Board of Directors of Southern Research. We involved both Boards in subsequent steps, the first of which was to obtain approval for the engagement of Stonecroft Capital to serve as an advisor in the process.

I was fortunate to have very supportive boards at both Brookwood and Southern Research. We had discussed the possibility of acquisition in the abstract from very early in the company's history, so we were prepared for the actual discussions. I was already starting to assemble a team to aid in such a process. I cannot emphasize too strongly how important it is to have a solid team for this process, in particular someone who can provide perspective that is one step removed from the day-to-day. At Brookwood, we were very fortunate to have a great team, particularly Tim Howard at Stonecroft, who was integral to every part of the deal structure and negotiations; Greg Curran of Maynard Cooper & Gale, P.C., who provided legal support; and Debra Bingham at Valeo Partners, who worked with Tim on the deal and who was instrumental in review of technologies, markets, and license deals.

Please elaborate to our readers the full process.

ART: With our advisors' help, we negotiated the best possible term sheet; when presenting it to the Boards of Brookwood and Southern Research, we also presented different alternative strategic directions and the associated economics. At the end of the day, the strong strategic fit of Brookwood with SurModics that would benefit our clients and employees, the willingness to commit to continued presence in Birmingham, AL, and attractive terms and economics resulted in direction by the Board to proceed with detailed due diligence and negotiate a definitive agreement.

We spent the next few months in formal due diligence and negotiations of the definitive agreement, ultimately resulting in the merger in August. I will note that face-to-face meetings with both the Southern Research Board and the SurModics team with Stonecroft Capital, Valeo Partners, and Maynard Cooper & Gale were extremely important to the deal execution.

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What is the strategic importance of the acquisition of Brookwood, and how will it play into SurModics' drug delivery strategy?

Bruce: We believe the acquisition has resulted in SurModics possessing a broad and unique set of capabilities in the drug delivery industry. We can now deliver small and large molecule drugs from coatings, implants, and microparticles. The acquisition expands SurModics' capabilities in local drug delivery while enabling us to enter the systemic drug delivery market, thereby creating new opportunities with pharmaceutical and biotech customers.

While strengthening our drug delivery efforts in our core cardiovascular, ophthalmic, and orthopedic markets, the addition of Brookwood also broadens our scope to the diabetes, oncology, dermatology, and psychiatric disorders markets, among others. We now also have a greater ability to satisfy the needs of our customers through enhanced product manufacturing capabilities and new proprietary platform technologies.

Overall, we view the acquisition of Brookwood as a very important part of our drug delivery strategy and are excited about the opportunities our combined efforts are creating.

Is there anything that surprised you about the process?

Art: It took longer than I expected. Initially, I had hoped to "conclude" within 60 days after execution of the term sheet. Our advisors correctly indicated that it would likely take double that (it did). The collaborative nature of the negotiations was also surprising as both parties seemed genuinely interested in finding solutions that worked and addressed respective issues. From my side, I was dealing with two Boards; this was an additional step and perhaps did lengthen the process, but I was able to obtain a broader perspective as a result. I was pleasantly surprised by how enthusiastically the Brookwood employees embraced the merger and the benefits it would bring to our clients.

Was there anything helpful in the process you would like to highlight for our readers?

Art: Among various things, I would have to say the Stonecroft Capital and Valeo Partners Team. Tim and Debra performed a formal valuation of the business. Because of their understanding of the drug delivery space, we were able to have this completed in a timely manner. This was important because it allowed management, our Board of Directors, and our parent to objectively evaluate the offer we subsequently received from SurModics. The Stonecroft team worked with SurModics' advisor to clarify and improve their initial offer to the point at which it could be brought forward for approval. Upon approval of the initial terms, they worked closely with our counsel to ensure the business terms of the deal were preserved in the definitive agreement and, most importantly, worked with the other side to work through issues that came up during the process. They were with me every step of the way, anticipating and helping to manage the issues that arise in every deal. Whenever we hit an impasse, Tim Howard, our lead banker, would work something out with his counterpart that worked for both parties. Again, the availability of Stonecroft for face-to-face meetings was invaluable. They were present early in the process to meet with Bruce and his SurModics team. Looking back, it was vital to have an advisor with the drug delivery and deal execution experience at the table with SurModics and Goldman Sachs.

How is life at Brookwood since the merger? Can it be labeled successful?

Art: One comment I made at a company meeting was that I was looking forward to being able to keep my office door open again! Obviously, a transaction takes some attention, and a number of the discussions are behind closed doors. We had a very successful integration process that is continuing and is obtaining broad involvement and buy-in from both Minnesota and Alabama. The most rewarding events over the past few months have been to introduce each other to a broader customer base. For example, Brookwood staff has begun attending more medical device meetings, and SurModics staff more pharma meetings, with cross-introductions.

We have received positive support from clients and prospective clients. As an example, a SurModics' client that Brookwood was also in late-stage discussions with was excited to hear of the acquisition. The client mentioned it was great news for them as it would be much easier to get the service and technologies they needed now that the two companies are part of the same team.

So what is the next challenge moving forward?

Art: The next major challenge for us is a great opportunity of expanding capabilities. We had initially started the process of raising capital to further support our current customers' needs by expanding manufacturing capacity. We are in late-stage planning for that expansion and look forward to the hard work throughout the next year to execute on that vision.

Are there more acquisitions on the horizon for SurModics in the drug delivery space?

Bruce: We continue to evaluate new opportunities in drug delivery and other areas, but it is a top SurModics priority to successfully integrate the two companies that we acquired this summer. ◆

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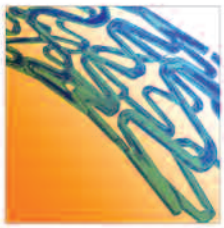

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The Obviousness Standard in a Post-KSR World

By: Clifford M. Davidson, Esq.

On April 30, 2007, the Supreme Court sent shock waves throughout the world of patents with its holding in KSR International v. Teleflex Inc., 127 S.Ct. 1727 (April 30, 2007). Suffice it to say that in this decision, the Supreme Court held that the Federal Circuit had been applying a flawed analysis with respect to the obviousness inquiry. In doing so, the Supreme Court called into question the motivation to combine references when undertaking an obviousness analysis, and further apparently resurrected "obvious-to-try" as a useful standard for determining obviousness of a patent claim. More detail is found in my previous article in the June issue of this publication. Now, the dust has settled somewhat, and the following will examine the fall-out of the KSR decision.

THE USPTO'S VIEW

Shortly after the issuance of the KSR decision, the deputy commissioner for patent operations at the USPTO (Margaret A. Focarino) issued a memorandum to the patent examiners. The Focarino memo included some important messages. First, she noted that the Graham factors for obviousness under 35 U.S.C. §103(a) are still in force. The Graham factors instruct one to determine the following: (1) the scope and content of the prior art; (2) the differences between the claims and the prior art; (3) the level of ordinary skill in the prior art; (4) secondary considerations, if any, of non-obviousness. It further noted that the Supreme Court did not completely reject the TSM test (teaching, suggestion, or motivation) for making a determination of obviousness. Instead, the Supreme Court rejected a rigid application of the TSM test, which would require an explicit showing of a teaching, suggestion, or motivation to combine prior art before holding a claim to be obvious.[1] The Focarino memo instructed the examiners to provide explicit analysis to explain the reason why multiple prior art references are combinable in the manner prescribed by the examiner. The full text of the PTO memo is found at http://pub.bna.com/ptcj/PTOMay3memo.pdf.

HOW HAVE THE COURTS BEEN AFFECTED BY THE KSR DECISION?

Just 1 week after the KSR decision, the Court of Appeals for the Federal Circuit (CAFC) had already adapted itself to the KSR decision and applied a "common sense" obviousness analysis in place of its previously rigid "explicit" TSM test. See *Leapfrog Enterprises, Inc. v. Fisher-Price, Inc.,* No. 06-1402 Fed. Cir. (May 9, 2007).

But how does the KSR decision affect pharmaceutical patent litigation? Although it is very early in the game since KSR was decided, there have been a number of recent decisions that provide us with some guidance.

THE COURT OF APPEALS FOR THE FEDERAL CIRCUIT

The Federal Circuit has considered the effect of the KSR decision on an obviousness determination in a recent case involving the blockbuster diabetes drug ACTOS®. The case was on appeal from the United States District Court for the Southern District of New York, where a bench trial solely on the issues of validity and enforceability of the API patent covering ACTOS (U.S. Patent No. 4,687,777) was not shown to be invalid under 35 U.S.C. § 103 [*Takeda Chem Indus., Ltd. v. Mylan Labs.,* 417 F.Supp.2d 341 (S.D.N.Y. 2006)]. The District Court decision had been entered prior to the KSR decision. The Federal Circuit's reasoned analysis in the *Takeda* decision is instructive as to how the Federal Circuit views the interaction between the KSR decision, its own body of work, and the *Graham* test.

The '777 patent claimed the active ingredient by virtue of its chemical structure. With respect to structurally similar compounds, the Court stated that "in order to find a prima facie case of unpatentability in such instances, a showing that the 'prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention' was also required" [*Takeda Chem Indus., Ltd. v. AlphaPharm Pty. Ltd. and Genpharm, Inc.* . . F.d (Fed. Cir. 2007)]. The Federal Circuit then went on to discuss the fact that while the Supreme

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Court in KSR rejected a rigid application of the TSM test in an obviousness inquiry, the Court did indicate there is no necessary inconsistency between the idea underlining the TSM test and the *Graham* analysis. Rather, the Supreme Court had acknowledged the importance of identifying "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does" in an obviousness determination. KSR at 1731. The Federal Circuit concluded that in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound." Id. at page 6.

A closer look at the prior art and the reasoning behind the decision is warranted. The closest prior art to the active compound in ACTOS (pioglitazone) was compound b, which was one of 54 compounds synthesized in a prior art Takeda patent (U.S. Patent No. 4,287,200). The parties did not dispute that compound b was the closest prior art compound, and compound b was in fact characterized in the prosecution history of the '777 patent as being "especially important." The District Court, however, disagreed. It considered compounds identified in a published article (Sodha II) to be closer art. Therein, three specific similar compounds were deemed most favorable in terms of toxicity and activity, and compound b was singled out as causing undesirable side effects (eg, causing an increase in body weight). To arrive at pioglitazone, one would have to make two changes to compound b: replacing the methyl group with an ethyl group (homologation) and moving the ethyl substituent to another position on the ring ("ring walking").

The Federal Circuit considered the aforementioned information and concluded the following:

. . . rather than identify predictable solutions for anti-diabetic treatment, the prior art disclosed a broad selection of compounds, any one of which could have been selected as a lead compound for further investigation. Significantly, the closest prior art compound (compound b, the 6-methyl) exhibited negative properties that would have directed one of ordinary skill in the art away from that compound. Thus, this case fails to present the type of situation contemplated by the court when it stated that an invention may be deemed obvious if it was obvious-to-try. The evidence showed that it was not obvious-to-try.

The Federal Circuit decision in the Norvasc® litigation was rendered months before the KSR decision. However, comments by certain judges in a Federal Circuit Decision not to rehear the case en banc did touch upon the KSR decision. More particularly, in *Pfizer, Inc. v. Apotex, Inc.* 480 F.3d 1438 (Fed. Cir. 2007), the Federal Circuit held that the patent claiming Pfizer's amlodipine besylate (active ingredient in Norvasc®) was invalid because a skilled artisan would have been motivated to combine prior art references to achieve the claimed invention and would have had a reasonable expectation of success, and further that it would have been obvious to optimize acid addition salt formulation for an active pharmaceutical ingredient in a hypertension drug (amlodipine besylate instead of amlodipine maleate).

In his dissent from the denial of rehearing en banc, Judge Lourie of the Federal Circuit stated the following:

These issues are of exceptional importance. Chemical and pharmaceutical compounds often can be found to be prima facie obvious because they are based on prior work that could reasonably suggest them, See KSR . . . but commercialization of such compounds may depend on their possession of unexpected properties. Such properties may be biological or physical. A failure to recognize all such properties that may be relevant to the value of such a compound may doom the compound to being poured down the drain rather than becoming an important therapeutic. General public, innovative companies, and ultimately generic companies depend upon faithful adherence to this principle. In addition, our cases hold that unexpected properties make for non-obviousness. . ., and this decision disdains such properties if they are not biological. That is a conflict with our precedent that needs resolution.

The issue to which Judge Lourie was speaking, that the panel mistakenly determined that the superior properties of the besylate salt did not overcome a prima facie case of obviousness because they showed no superior therapeutic (biological) value, was furthered by the dissent of Judge Rader.

IN THE U.S. DISTRICT COURTS

Two weeks after the KSR decision, a judge in the U.S. District Court for the District of Maryland gave jury instructions in a biotech case that advised the jury that it could find the disputed patent invalid for obviousness under the obvious-to-try standard that was given a fresh breath of life in KSR. In that case, which involved a genetically engineered enzyme for cloning DNA, the jury nevertheless held the patents' validity. It was particularly noteworthy that the judge agreed to stress in his instructions that the jury should not use hindsight to find the invention was obvious-to-try, and that such a finding would only be proper if that which was considered to be obvious-to-try was ultimately successful, noting in his instructions that arts, such as biotechnology, are not generally predictable [*Invitrogen Corp. v. Clontex Laboratories, Inc.,* D.Md. No. AW-96-4080 (May 16, 2007)].

The KSR decision also came into play in the end of ANDA litigation concerning Pepcid® Complete, an OTC acid indigestion product. In that case, McNeil asserted its U.S. Patent No. 5,817,340 covering the combination of famotidine and antacids, and the use of an impermeable coating against the generic product. Following a 9-day bench trial, Judge Pauley of the U.S. District Court for the Southern District of New York found that the '340 patent was invalid for obviousness. Judge Pauley concluded that all of the relevant limitations in the claims of the '340 patent were found in the prior art,

and that the '340 patent had done nothing more than combine the predictable results of two prior art references (regarding a chewable tablet) with the predictable results of two other patents (regarding taste-masking). The judge cited KSR frequently in his decision, while stating that it did not change the result of his analysis in this case. In view of the strong showing of obviousness, the judge also held that the secondary considerations patentability, such as commercial success, could not overcome the invalidity of the claims.

In *Abbott Laboratories v. Sandoz, Inc.,* slip opinion, 2007 WL 1549498 (N.D.Ill.), Sandoz asked the Court to stay enforcement of a preliminary injunction it had issued shortly prior to the KSR decision. At issue here is the ANDA filing by Sandoz for Biaxin® XL. Abbott's U.S. Patent No. 6,010,718 included claims directed, eg, to an extended-release erythromycin derivative in the gastrointestinal environment, comprising the erythromycin derivative and 5% to 50% polymer, so that when ingested orally, the composition induces statistically significant lower mean fluctuation index in the plasma than an immediate-release version of the drug, while maintaining substantially equivalent bioavailability.

The gist of the Sandoz position was that the KSR decision rendered the preliminary injunction order reversible. The Sandoz position centered around the combination of a patent that disclosed the use of an alginic acid polymer in making sustained-release formulations (including Clarithromycin) and a patent publication disclosing sustained-release formulations of azithromycin in general (and including the use of HPMC as a polymer). Sandoz argued that the combination of these references along with the FDA definition of a term "bioequivalence" would have motivated a person of ordinary skill in the art to combine these sources of information to arrive at an extended-release clarithromycin product (solving a known problem).

The Court disagreed before the KSR decision (by granted the prelminary injunction) and after the motion for stay of enforcement of the preliminary injunction after the KSR decision. The Court found that Sandoz had not produced evidence indicating that the pharmacokinetic limitations were disclosed in the prior art or were inherent to the structural limitations of the prior art compositions. After a thorough discussion of the KSR decision, the Court stated that "the need to demonstrate the presence of all claim limitations in the prior art (when the legal theory is based on obviousness due to the combination of prior art teachings) has not been obviated" by the KSR decision. A crucial finding by the Court was that a person skilled in the art would not be motivated to interchange clarithromycin in one reference for azithromycin in the other reference because the prior art clarithromycin patent did not disclose the claimed PK profile.

WHERE DO THESE DECISIONS LEAVE US?

While it certainly does appear that the courts have duly noted the KSR decision, and have taken particular care in providing the bases for determining motivation to combine references in recent decisions, it does not appear that there will be any drastic change in the way courts review patent claims. It does appear that the "unexpected result" basis for patentability remains a strong force in overcoming an argument of a motivation to combine prior art references. On the other hand, it is still too early to tell what effect the KSR decision will have on patent examiners at the USPTO. One may guess that experienced examiners will tend to continue to examine patent claims in the manner they have done so previously, but perhaps with more attention to the necessity to provide an explanation as to motivation to combine references. Less experienced patent examiners may jump on the KSR bandwagon and slow the already time-challenged review of patent applications to a crawl. ◆

REFERENCE

1. Indeed, there was never a requirement that a result of the TSM test required explicit teaching, suggestion, or motivation to combine prior art to make a determination of obviousness of a claim.

BIOGRAPHY

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

When Developing a Drug Delivery Device, Time is of the Essence

By: Jay Bhogaita, MS, MBA

The general principles and benefits of Accelerated Feasibility Testing (AFT) are well known to many pharmaceutical companies, those being an efficient and timely assessment of the appropriate drug delivery method for your formulation; accelerating the device development phase and ultimately, minimizing time to market.

What is perhaps less well recognized, and is the focus for this article, are the particular benefits that an experienced specialty medical device manufacturer can bring to the development process in terms of timely objective advice, a cost-effective methodology and critically, real-world expertise in managing the complex relationship between the formulation and the device. For example, the interactions between a metered dose inhaler (MDI) valve, actuator, formulation, and container pack.

The successful pairing of a drug and delivery device is critical to the safety and efficacy of the product and usually its commercial success. Harmonizing these elements can be complex, requiring several iterations and consuming time and money.

In both established and emerging markets, AFT is helping pharmaceutical companies develop alternative methods of delivery using inhalation technologies, and the following will explore the particular benefits that AFT can bring to help speed the progress of such innovation.

WHY OUTSOURCE YOUR AFT PROGRAM?

Traditionally, the concept of outsourcing any element of the development process has been perceived by pharmaceutical companies as bringing risk and complication. There are naturally concerns around sharing commercially sensitive information, such as a sense that ownership of the project will be lost, the company entrusted with that element of development may not meet all the regulatory requirements for launch, or simply that the cultural differences and working practices of the two companies mean that outsourcing is a less than straightforward affair.

The reality can be quite different, but there are criteria by which potential partners should be measured. Their facilities, experience, technical capability, procedures, and track-record are all factors that should be considered. There must also be a meeting of minds both culturally and scientifically and a mutual commitment to developing and building a strong relationship. Such a close relationship can deliver many benefits, such as much faster development time, perhaps enhancements to formulations, and often a much more robust product.

TABLE 1

THE KEY CRITERIA TO OUTSOURCING YOUR AFT PROJECT

1. What kind of relationship are you looking for?
2. How complex is the device?
3. Do you have the necessary Container Closure System expertise in-house?
4. Do you have the required resource in-house?
5. Do you have expertise in marrying formulations with devices in-house?
6. Has the supplier got a track-record in your delivery device?
7. Can they demonstrate success with similar products?

WHEN TO OUTSOURCE DEVELOPMENT?

A lack of resources is often cited as a reason to outsource a development project or an element of the program. Although perfectly legitimate, the consideration to outsource should not be confined to times when internal resources are limited. Most expertise comes with experience, and companies should reasonably expect to see evidence that the selected outsourcing partner has successfully developed other devices from a similar phase as their own before committing to any part of a program. Bespak, a leader in medical devices for inhaled drug delivery and anesthesia, for example, has the facilities and, perhaps more importantly, the real-world expertise to optimize the complex relationship between the valve, actuator, can, and formulation. Only by truly understanding each element can the overall device be expected to meet the appropriate regulatory standards to reliably and effectively treat patients. When the value of such domain-specific knowledge is appreciated, the justification to outsource becomes much stronger.

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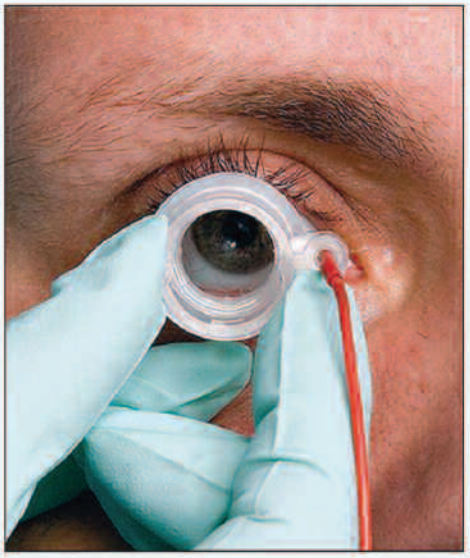

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Compared to in-house development, the services of a specialty medical device manufacturer can provide particular benefits for those organizations that wish to develop an inhalable form of an existing active pharmaceutical product, or that wish a rapid transition between dosage forms.

THE COMPLEX RELATIONSHIP BETWEEN DRUG & DEVICE

Often with in-house development programs, the Container Closure System (CCS) and actuator are considered in isolation of the formulation. This can lead to a trial-and-error approach when it comes to optimizing the valve and actuator for the specific formulation; an iterative process that has been known to extend development times by months or even years. As an illustration, a number of standard valves could be tested with a particular formulation in series, and yet none of them prove to be compatible. By developing the formulation in parallel with a delivery device and with a thorough understanding of the characteristics of the formulation, the manufacturer's AFT scientists can optimize valve and actuator within a much shorter timescale.

Device designers can also benefit from a manufacturer's AFT process, from initial material specification to the overall efficacy of the medicinal product. It is a recognized feature of the US Food and Drug Administration (FDA) regulatory approval process that the decision to select materials made in the early years of a device's development are expected to be fixed for the lifetime of that device. If a specific material is used in device development and the critical safety and efficacy studies have begun, a change in any part of the specification may necessitate additional testing and delay the product's development and launch and potentially result in fewer sales. A device manufacturer should have experience in working with medical-grade materials, preferably ones that have been previously used. The manufacturer can then help the marketing authority select the most appropriate material for their formulation and device.

Successful and profitable commercialization is best fulfilled if the device can be produced cost effectively over time. By working closely with AFT specialists who are closely aligned with manufacturing engineers, any foreseeable problems that may otherwise hinder successful industrialization and commercial production of the device can be addressed at the start, saving valuable time and money later.

DEVELOPING NOVEL METHODS OF DELIVERY USING INHALATION TECHNOLOGIES

While much of the AFT offer is focussed on optimizing existing therapies and devices, manufacturers with AFT capabilities can also help speed the development of novel device concepts. Nasal drug delivery is one example in which a manufacturer with specific knowledge can help customers take advantage from a new delivery technology. The nasal cavity provides several benefits as a target for drug delivery, including the rapid onset of therapies and the capability to deliver delicate or complex molecules, such as peptides and proteins. The efficient delivery of drugs to the nasal region, however, is highly complex and benefits from a thorough understanding of the nasal anatomy, as well as AFT in order to optimize a device. Bespak has invested in the development of a nasal cast designed to replicate the structure and complexities of the nasal cavity. The nasal cast can then be used to characterize how aerosolized particles are deposited within the nasal region as device features, fire points, and formulation characteristics are varied.

OPTIMIZING EXISTING TECHNOLOGIES TO PROVE A POINT OF DIFFERENCE

Though MDI technologies typically offer cost-effective benefits and generally pass through the regulatory approvals process relatively quickly, there may be occasions, particularly in the generics market, where the transfer of a MDI therapy into a Dry Powder Inhaler (DPI) may enable customers to create a point of difference through enhanced device design or a clearly differentiated brand. A device manufacturer with credibility in optimizing both kinds of device can offer real benefits in terms of delivering modern DPI designs that provide much sought-after design and patient compliance features.

SUMMARY

AFT is a well-established methodology with clear benefits to pharmaceutical partners and device designers in terms of identifying an appropriate drug delivery method and then accelerating the device development phase. This article has presented the additional benefits of using an experienced specialty medical device manufacturer with real-world expertize in managing the complex relationship between valve, actuator, formulation and drug pack. While much of the AFT process is focussed on optimizing existing therapies and devices, device manufacturers can also help speed the development of novel, conceptual devices.

BIOGRAPHY

Mr. Jay Bhogaita is the Commercial Director at Bespak, with specific responsibility for the company's AFT offer. Prior to joining Bespak in 2002, Mr. Bhogaita led Avon Rubber's Elastomer formulation program before joining Valois' UK Pharmaceutical Division. He earned his MBA from Henley, has an MS in Polymer Science, an LLP law degree and a BSc in Chemistry.

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Partnerships: The Key to Combination Product Success

By: Christine M. Ford, MBA

In no other area of the life sciences is partnering as critical as it is in the development of combination products. According to Veronika Litinski, Director, MaRS Venture Group, "Combination products have to be better than the sum of their parts." This underscores the fact that there are numerous challenges inherent in the design and development of a combination product. The best skill sets from not one, but multiple partner companies are often required to bridge the divide between a good idea and a successful product.

For example, whereas engineers possess processing, testing, and manufacturing knowledge, they often lack the scientific understanding of pharmacogenomics, systemic toxicity, and animal models that is essential for the development of these products. Because it is not likely that expertise in all aspects of pharmaceutical development, analytical skills, medical device engineering, quality control, and delivery systems will be housed in a single company, the need to partner early on in the product development process cannot be overstated.

WHAT'S DRIVING THE COMBINATION PRODUCT MARKET?

Combination products enable pharmaceutical companies to extend the life of their products by combining approved drugs with a biologic and/or device, effectively creating a new patent. And with an estimated $100 billion worth of brand name drugs set to go off patent by 2010, patent extensions represent a major opportunity to recoup blockbuster success for pharmaceutical companies.[1] In addition to providing an effective product life cycle management strategy, combination products can also breathe new life into failed pharmaceutical products. For example, a product that exhibited systemic toxicity as a pharmaceutical drug may demonstrate good efficacy locally, making it ideal for use in a targeted drug delivery combination product.

THE RIGHT PAIRING OF EXPERTISE

The first step to establishing a combination product development partnership is to identify the right partner or partners. As partnerships are often formed out of the need to gain expertise where it is lacking, companies will often come together based on their respective strengths and weaknesses.

Combination product development partners will typically establish in-licensing and out-licensing agreements, which protect the purchase and sale of proprietary IP between companies. In some cases, companies will establish a joint venture, merger, or acquisition to develop a combination product.

When partnering, companies must take into consideration the different methodologies, terminology, and backgrounds of the staff involved. They must establish the proper project governance, team structures, and functional involvement needed for combination products. Corporate strategy, culture, and goals must also be in alignment with or complement one another.

For example, partner companies must be in agreement on speed of action, formalities in the contracting process, and timing of approval. If one company is targeting an FDA approval date of March 2008 and the other is projecting an approval date in April of the following year, then conflicts will surely arise throughout the development and FDA application process.

While synergy is specific to the parties involved, it has been said that biotechnology companies and device companies work better together. This may be attributed to the fact that biotechnology companies are more flexible and adaptable in their approach to working with other companies. The fact that biodevices are the fastest growing segment of the combination products market seems to underscore this synergy and the scientific efficacy of this type of combination product.

AVOIDING PARTNERSHIP PITFALLS

Because drug, biologic, and device developers traditionally use varied terminology even for similar processes, miscommunication is all too common among combination product development partners. A shared process that creates a standard approach and standard terminology throughout the organizations can go a long way toward bridging this communication gap.

It is also important to consider whether a potential partner company is mature or growing. Start-up companies may offer innovative ideas and superior R&D capabilities, but do they have the resources to see the product to completion? While mature companies tend to be more financially stable, they may lack the ability to innovate and may be less flexible to work

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with. For this reason, it is critical to perform due diligence of intended partners.

IP PROTECTION CONSIDERATIONS

As an integral component of any combination product development alliance, IP protection can be very complicated because it can apply to materials, methods of making the device, the device itself, methods of using the device, and integration of the device into larger systems.

The most important aspect of developing an IP strategy is the communication between business, legal, technical, and marketing departments within an organization. Without this communication, it is difficult to align the development of the IP portfolio with the business objectives of the organization, creating the risk of ad-hoc IP development.

Before and after entering a partnership, it is important that all participants have a clear understanding of their own IP position and objectives, and those of their collaborators and contract manufacturing partners. All parties should understand who owns current and future innovations or trade secrets, who is responsible for documenting the innovations and know-how through publications and other records, and who will be filing any needed patent applications.

A strong IP portfolio can serve as a bargaining chip in requests for shared royalties, or as a trading card in negotiations among partners. To gain transaction leverage in such negotiations, it's critical to have IP documentation that discusses the combination product itself — its current and potential uses and how it might be used with other products. Quite simply, companies that have a stronger IP position — backed up with well-founded documentation — are likely to get a better deal in the combination product marketplace than they would without it.

Developers should also be aware of the potential dichotomy that may arise between IP protection and regulatory choices when submitting combination product inventions to the United States Patent and Trademark Office (PTO). Because the patent application must describe the invention's Primary Mode of Action — the single mode of action of a combination product that provides the most important therapeutic action of the combination product as defined by the FDA — care must be taken to accurately describe the product's therapeutic effect. The FDA will later use those statements when assigning the product to the Center for Biologics Evaluation and Research (CBER), Center for Drug Evaluation and Research (CDER), or the Center for Devices and Radiological Health (CDRH).

THE ROAD AHEAD

Given the tremendous potential that combination products represent from a life-saving and product life cycle management perspective, it is not surprising that just about every multi-billion dollar pharmaceutical and medical device company has combination product development plans in their future.

Some of the most promising areas of development are drug delivery products and innovations in regenerative medicine, in which biomaterials, growth factors, and even cell therapies are combined. Leveraging proven technology from the IT and telecommunications industry, nano-enabled devices are also poised for growth along with neuro-modulating devices, which promise to advance the field of neuromedicine.

As combination products grow in complexity, so will the partnerships needed to create them. Today's combination product development partnerships are expanding to include an increasing number of partners, including pharmaceutical companies, biotechnology companies, and medical device companies along with organizations that perform contract manufacturing and other outsourced functions, such as sterilization. The good news is that development partners are getting smarter about designing combination products, enabling them to effectively overcome scientific, regulatory, and business roadblocks to speed new innovations to market.

REFERENCE

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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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Hydrocapsules®: A New Method for Aqueous Drug Delivery

By: Ara Manukian and William Toreki, III, PhD

ABSTRACT

A new encapsulation technology developed by Analytical Research Systems, Inc. (ARS Inc., Gainesville, FL) with funding support from the USDA SBIR Program Office provides for a unique method of encapsulating a wide range of aqueous-based liquids with a cross-linked polymeric outer shell that can be used to deliver nutrients, vitamins, drugs, vaccines, and other chemical compounds. The method, originally developed for use in encapsulating aqueous-based solutions for entomological and agricultural applications, has the special capability of encapsulating live beneficial organisms, tissues, viruses, cells, bacteria, and fungi that need to be stored and delivered in aqueous solution. The liquid-filled capsules produced by this method are called Hydrocapsules® and have many potential applications in both veterinary and human pharmaceutical, medical, and dental sciences.

INTRODUCTION

The Hydrocapsule method allows for the formation of mononuclear microcapsules of the shell-core type that are produced by a patented process of simultaneously extruding an inner liquid core (encapsulant) material along with a continuous outer coating or layer of a polymerizable liquid (capsule shell), which is substantially immiscible with the inner liquid core, through concentrically aligned extrusion nozzles to form spherically layered bi-liquid droplets. These droplets are then subsequently exposed to energy input from high-intensity ultraviolet (UV) light, which causes the polymerization of the outer shell layer by the process of UV-initiated free-radical chain polymerization of functionalized pre-polymers and/or vinyl monomers. The resulting capsule shell material is a cross-linked hydrophobic elastomeric polymer network, which can have various physical and chemical properties depending on the formulation and application requirements. The capsules formed by this method are called Hydrocapsules, which implies that they have an aqueous liquid core surrounded by a thin hydrophobic polymer membrane; however, they are capable of containing a variety of liquid materials having a composition ranging from completely aqueous to completely non-aqueous, and typically range in size from a couple of hundred microns to several millimeters in size (Figures 1 & 2).

The capsule coatings produced with this Hydrocapsule method include a wide range of cross-linked polymers (many of which are FDA approved). These coatings can include a wide range of reactive or non-reactive components within the polymer matrix that can create a controlled or triggered release, swelling, or total breakdown of the capsule shell to deliver its contents. These release "mechanisms" can be designed into the polymer coating (shell) in such a way that it can react to changes in the surrounding environmental conditions to cause a breach of the coating, or in other instances, cause a transformation in the physical properties of the polymer coating that would allow for the diffusion or permeation of the contents through a softened or swollen shell. For pharmaceutical applications, some of these release mechanisms can include acidic or alkaline pH-sensitive triggers built into the polymer matrix.

Truly unique to this Hydrocapsule technology is the ability to encapsulate 100% water or other high aqueous-content mixtures that are not currently available in typical pharmaceutical capsule, softgel, or hard pill manufacturing. It should be noted that this process can equally encapsulate totally non-aqueous solutions, such as oils, other high-lipid concentration or emulsified liquid mixtures, sugar solutions, and alcohols with small amounts of water, which albeit, can be done by other types of industry-standard processes, such as the familiar "Softgel" technology used to encapsulate vitamin E, Omega-3 fish oils, and other oil-soluble drugs. However, these processes and are not suitable for encapsulating high concentrations of aqueous liquids, and unlike the"Softgels" and other similar products, Hydrocapsules can provide a stable capsule for long-term storage solution in the presence of high levels of external moisture (humidity) or water.[1]

HISTORY OF DEVELOPMENT

Encapsulation is commonly used to describe the process whereby an active ingredient is placed into a stabilized form in order to allow it to be conveniently

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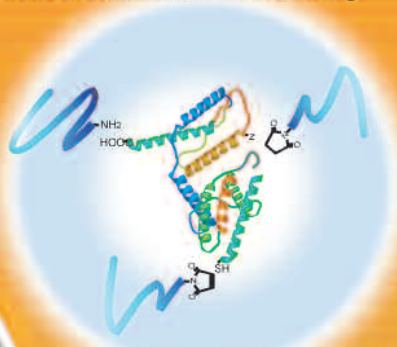
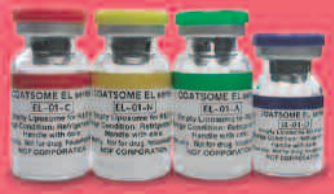


PEG-DRUG



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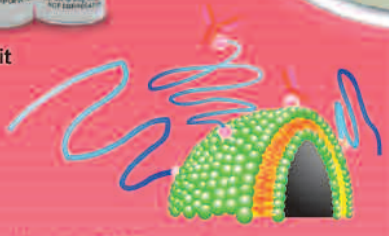

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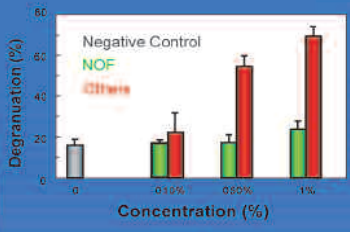

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stored or protected from unfavorable conditions until needed. The active ingredient may be dispersed in a protective matrix, or it may be surrounded by a coating, a shell, or a membrane. The release of active ingredient(s) from the protected form may be rapid (such as by crushing or by ingestion), or gradual (such as by dissolution, diffusion, chemically triggered or controlled time-release, or biodegradation). In this manner, it is possible to maximize the effectiveness of the active ingredient by ensuring it is released at the proper time. This "controlled release" can also be made to occur over a programmed time interval (sustained release) or on demand (stimulated release).

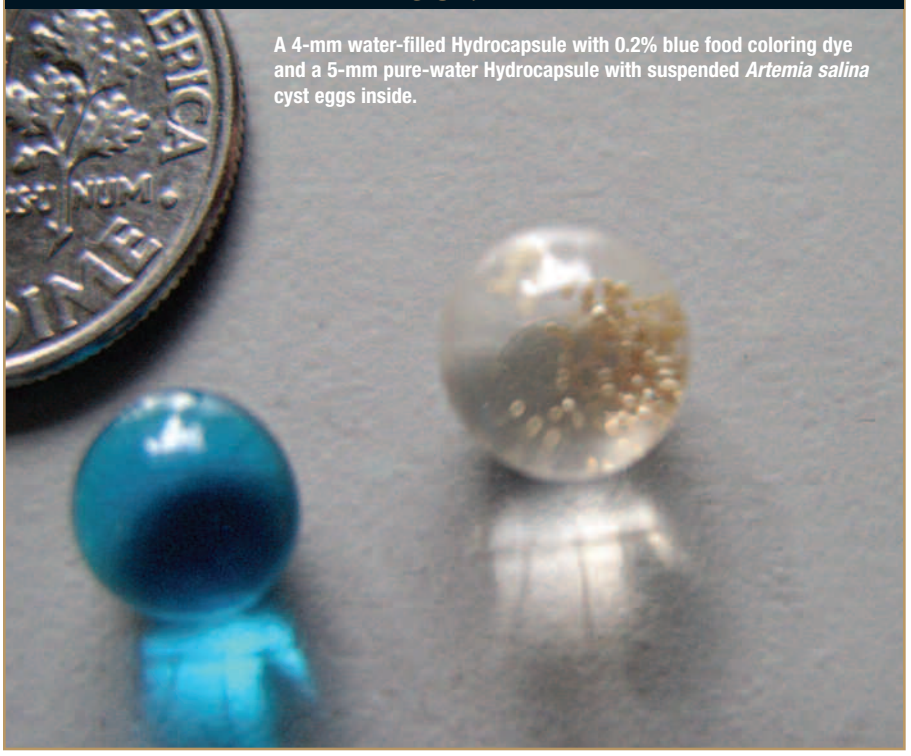
The term "microcapsule" has been used to describe small particles or beads, which range in size from less than one micron, up to several millimeters, which may contain a wide variety of active ingredients.[2-6] Microcapsules can be divided into two broad groups.

The first is Aggregate type microcapsules, which have the active ingredient dispersed uniformly throughout a continuous matrix. The matrix may be a solid dry polymer or a gel swollen with solvent. In the case where the gel is swollen with water, the term "hydrogel" is applied. Hydrogel encapsulation systems of this type are generally based on water-soluble polymers, such as alginate, gelatin, pectin, agar, gellan, or starch.[7]

The second is Mononuclear microcapsules, which consist of materials that show a true "shell-core" morphology. These are similar to an egg in that they have a solid outer shell or flexible membrane surrounding a core that may be a liquid, a solid, a gel, or a combination of any of these. Hydrocapsules fall into this second category.

Methods of producing microcapsules are the subject of numerous books and articles; however, the majority are simply not suitable for producing medium-to-large size (> 500 microns in diameter) mononuclear microcapsules with a true shell-core morphology and capable of containing an aqueous-based liquid core solution.[2-6,8,9] The method of "concentric extrusion" can be used to produce this type of microcapsule, in which two mutually immiscible liquids are simultaneously extruded through concentric

FIGURE 1



A 4-mm water-filled Hydrocapsule with 0.2% blue food coloring dye and a 5-mm pure-water Hydrocapsule with suspended *Artemia salina* cyst eggs inside.

orifices in order to produce a bi-liquid column, with the core fluid on the inside. Under the influence of gravitational, surface tension, or other forces (centrifugal, pressure, etc.), this bi-liquid column fragments into discrete droplets having a shell/core morphology. The liquid outer shell is then made to undergo a physical/chemical change via various controlled mechanisms enabling the liquid core to have a specifically engineered shell ranging from elastomeric and/or permeable to completely hard and impervious to liquids. Hardening of the shell is generally effected by heating to remove a solvent or by cooling to solidify a molten shell material. The outer coating in these systems is often a molten wax or a solution of aqueous polymer, such as gelatin or alginate. The use of heat, to melt the shell material or to drive off solvent can be detrimental to sensitive core materials, such as protein solutions or suspensions of living organisms. Additionally, the use of solvent-based shell formulations can lead to undesirable contamination of the core material as well as health and safety concerns.

Aqueous-based shell formulations, such as gelatin, cannot be used in conjunction with aqueous core materials because phase incompatibility is a necessary prerequisite for formation of a shell/core morphology using this technique. Also, these types of shells are, by nature, easily affected by water and also very susceptible to dehydration. Another drawback of other existing liquid encapsulating techniques is that the physical and mechanical properties of the shell materials suitable for use in these approaches are limited. Waxes, for instance, have very poor elasticity and mechanical strength and also low melt viscosity, making production of very thin membranes impractical. Low molecular weight thermoplastic polymers are generally too brittle and lack the flexibility to give strong, thin-walled, individual capsules. Thin, flexible, and durable membranes are generally only associated with cross-linked elastomeric polymers, which are generally insoluble and will not melt into a flow-able liquid even at extreme temperatures.

The initial application that lead to the development of the Hydrocapsule technology was brought about by a need to encapsulate high-protein content, aqueous-based, artificial liquid nutrient diets by Dr. Patrick D. Greany at the USDA's Agriculture Research Services, Center for Medical and Veterinary Entomology (CMAVE) based in Gainesville, FL. The USDA needed to encapsulate these nutritional diets for the purposes of feeding beneficial entomophagous insects (good insects that eat pest insects) so they could be mass reared economically in large numbers so they could be subsequently released into

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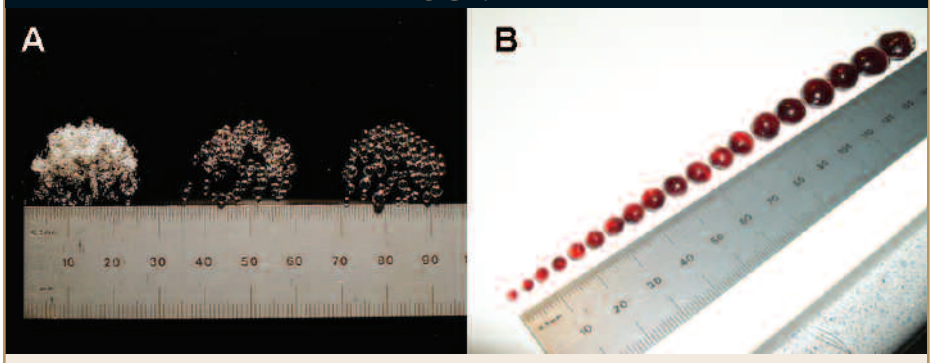
FIGURE 2



Various-size (A & B) Hydrocapsules ranging from 200 microns to 10 mm in diameter.

agricultural settings for natural control of phytophagous pest insects (plant-eating insects). This concept of releasing large numbers of beneficial insects to augment already-existing populations of beneficial insects is called Augmentative Biological Control (ABC), and is one of several Insect Pest Management (IPM) strategies being employed by the USDA to help decrease the usage of traditional chemical pesticides in agriculture. ARS submitted a Small Business Innovative Research (SBIR) Phase I grant proposal to the USDA and was funded in 1996. Subsequently, ARS was awarded an SBIR Phase II grant, and follow-up Phase III funding was provided by commercial partners to complete development of the Hydrocapsule technology. US and international patent applications (PCT) were filed in 2000, and the US Patent was awarded in 2004 (US Patent No. 6,780,507 B2) along with the US Trademark Hydrocapsule®.

THE HYDROCAPSULE PROCESS

The Hydrocapsule process comprises two critical steps: (1) the fluid-mechanical process of co-extruding two immiscible liquid streams (the outer shell and inner core liquids) to form a bi-liquid column and subsequent droplets; and (2) the chemical reaction to polymerize the outer liquid shell material to convert it to a solid coating that surrounds the liquid core.

In the first step, the process of co-extrusion involves ejecting two liquid streams from concentric nozzles under a force. In this manner, the liquid solution to be encapsulated and an immiscible shell-forming organic liquid are pushed simultaneously through concentric nozzles by force. The center nozzle carries the liquid material to be encapsulated, while the outer nozzle carries the coating precursor. The choice of orifice size will vary depending on the particular materials and final capsule size selected. The use of larger-diameter nozzles will generally result in the formation of larger Hydrocapsules. After emergence from the concentric nozzle, a series of concentric bi-liquid droplets is formed and then enter into a reaction zone (Figure 3). Inside this reaction zone, energy input from a high-intensity mercury lamp is used to supply UV light to catalyze, initiate, and promote the curing and free-radical chain polymerization of the vinyl monomers, oligomers, pre-polymers, and cross-linking agents, which are the typical components of an outer shell formulation. Under the influence of gravity, the bi-liquid stream will break-up into multiple smaller discrete droplets. This effluent enters into a column with a suspending medium that provides some buoyancy. The main purpose of the suspending medium (which can be a liquid or gas) is to slow the gravitational descent of the droplets, which increases the residence time in order to allow the polymerization, solidification, and/or cross-linking reactions to proceed to substantial completion, and aids in droplet separation.

The second step, polymerization of the hydrocapsule shell, is accomplished via free-radical chain polymerization of vinyl monomers utilizing photo-initiators, which rely on the absorbance of light energy in order to produce free radicals, which then initiate the polymerization of reactive vinyl groups present in the shell formulation. In this process, UV sensitive photo-initiators are used (such as benzophenone, benzoin ether, camphorquinone, and acyl phosphine oxide), which react within seconds. The concentration of photo-initiator used in the shell-forming liquids varies but is typically in the 0.1% to 2% weight range.

Selection of the proper shell components (formulation) is critical to completing the second step in the process. There are many shell-forming materials that are useful in making Hydrocapsules and can be selected from the broad class of vinyl compounds. These are compounds containing one or more polymerizable vinyl (-CH=CH_2) groups. These vinyl-containing shell-forming materials may be relatively low molecular weight compounds (< 200 amu), which are generally referred to as "monomers," or they may be larger molecules (> 200 amu), which are generally referred to as "reactive oligomers," "macromonomers," or "prepolymers." Thousands of such compounds are known, and there is a myriad of formulations, blends, and mixtures that can be useful. Typical low molecular weight monomers used in this process are methyl methacrylate (MMA), acrylic acid (AA), butyl acrylate (BA), hexyl acrylate (HA), and hydroxyethyl methacrylate (HEMA). Additional less-common acrylic monomers like long-chain alkyl acrylates and methacrylates (such as C_{12} - to C_{24}- acrylates), tetrahydrofuranyl acrylate, or caprolactone acrylate are used to impart useful properties to the shell formulation. Other commonly known vinyl monomers used are vinyl chloride, styrene, and vinyl acetate. Depending upon the application requirements of the shell, formulations can also include difunctional and multifunctional compounds (containing two or more vinyl units per molecule), such as divinyl benzene (DVB), ethylene glycol dimethacrylate (EGDMA), trimethyloyl triacrylate, and hexane diacrylate. Such polymers have desirable properties like good mechanical strength, elasticity, toughness, and flexibility.

Non-reactive components can also be incorporated into the shell formulations. These types of compounds do not react with the vinyl groups present, but instead are added to impart some type of desirable property to the shell-forming liquid (such as viscosity control) or to the final shell polymer (such as a plasticizing effect). Such compounds may be of any molecular weight. The use of non-reactive

polymers in the shell formulation will result in a polymer blend or interpenetrating network after the reactive vinyl components have undergone polymerization. Volatile components can also be added in order to facilitate processing or to modify the properties of the final shell materials. Other types of commonly used polymer additives, such as chain-transfer agents, antioxidants, anti-static compounds, UV stabilizers, dyes, and fillers can also be incorporated into the shell-forming fluids.

The use of silicone-based UV-curable elastomers as shell-forming components are particularly useful in making biocompatible capsules having favorable mechanical characteristics, environmentally benign properties, and desiccation resistance far superior to hydrogel-based polymers, such as alginate or gelatin (> 100X). Silicone polymers are commonly known to have, by far, the highest oxygen permeability of any class of synthetic polymer.[10-12] The oxygen permeability of silicone is 100 times that of polyethylene (PE). This is why it is particularly suited for applications such as gas-exchange membranes in heart-lung machines.[11] Many formulations are possible using reactive silicones blended with selected acrylic and urethane resins. Conversely, polymers like poly-vinyl chloride (PVC) or poly-ethylene terephthalate (PET) have very low oxygen permeability.[10,12]

CURRENT APPLICATIONS

The original application of this technology successfully demonstrated its first use in commercial applications to produce approximately 2- to 4-mm diameter hydrocapsules containing an aqueous-based liquid artificial nutritional diet used for the mass-rearing of beneficial insects that contained proteins, carbohydrates, and lipids, which were derived from processed animal livers along with added vitamins and antioxidants. The preparation of this and similar diets are described in detail in US Patent Nos. 5,799,607 and 6,129,935. A shell precursor solution was prepared by mixing a commercial aliphatic polyurethane acrylate composition (10 parts), a mixture of monofunctional acrylate monomers (15 parts: 50/50 caprolactone acrylate and tridecyl acrylate), a low viscosity aliphatic diacrylate oligomer (5 parts), a dialkyl phthalate plasticizer (10 parts), and a photo-initiator (1 part, benzoin isobutyl ether). The specific gravity of this mixture was measured and found to be approximately 1.04 g/cc. The capsule walls had an average thickness of about 50 microns and were generally soft and pliable such that the beneficial insects that were presented these hydrocapsules (*Podisus maculiventris and Diapetimorpha introita*) easily penetrated the shell and consumed the contents.

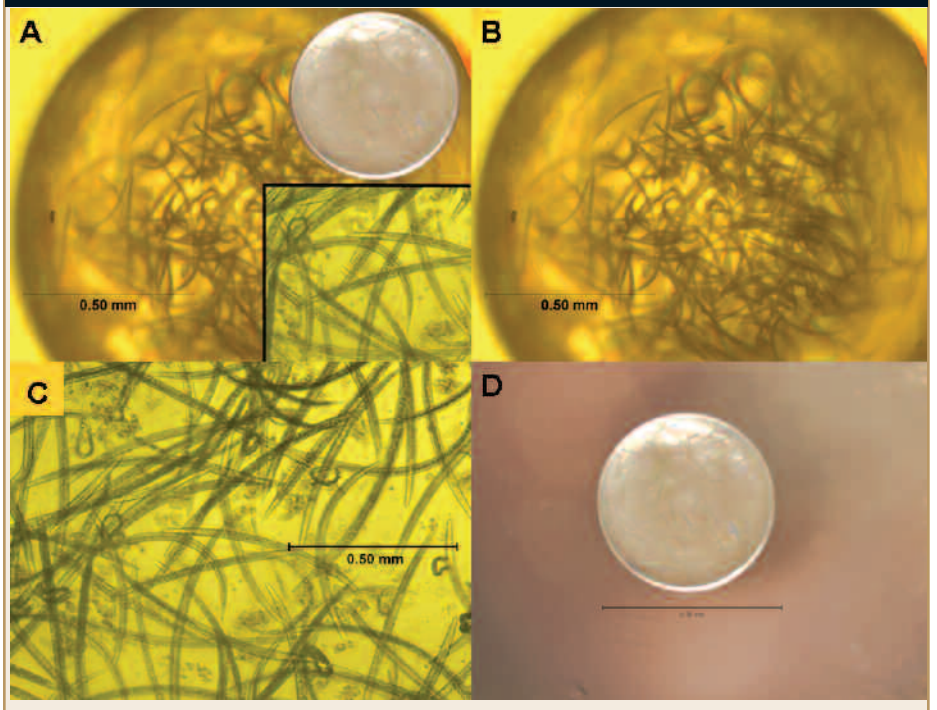
Subsequent work during this time was done on encapsulating and delivering attractant (bait) solutions, entomopathogenic nematodes, bacteria, and fungi for pest insect control. Production of hydrocapsules that contained an aqueous suspension of entomopathogenic nematodes (*Steinernema feltiae*) at a concentration of 2,000 AU/ml provided by a commercial supplier (BioLogic, Willow Hill, PA) were encapsulated in a solution of sucrose (40 g/L) and dextran (1 wt %) in de-ionized water (Figure 4). The specific gravity of this nematode suspension was measured and found to be approximately 1.008 g/cc. A shell precursor solution was prepared by mixing a commercial aliphatic polyurethane acrylate composition (6 parts), a mixture of monofunctional acrylate monomers (11 parts), an acrylate-functionalized silicone (6 parts), a dialkyl phthalate plasticizer (6 parts), and a photo-initiator (0.7 parts). Capsules were produced in a manner similar to that previously described. Microscopic examination of these capsules revealed they contained living nematodes. Capsule diameters ranged from approximately 2 to 4 mm. These capsules were stored in a loosely capped plastic vial in a refrigerator at approximately 5°C. After 9 months of continuous refrigerated and oxygenated storage, it was observed that the majority of the encapsulated organisms were still alive as evidenced by their swimming motions (active movement) when viewed under a 20X optical microscope.

Using the same formulations and procedures, an encapsulation of a commercial bacterial pesticide formulation (Thuricide® HPC, purchased from Home Depot),which is essentially a suspension of the entomopathogenic bacterium *Bacillus thuringiensis kurstaki* (otherwise known as BT), was also performed. The activity of this suspension was listed at 4,000 IU/mg. The capsule shell formulation was similar to the one described earlier. Capsules with an

FIGURE 3

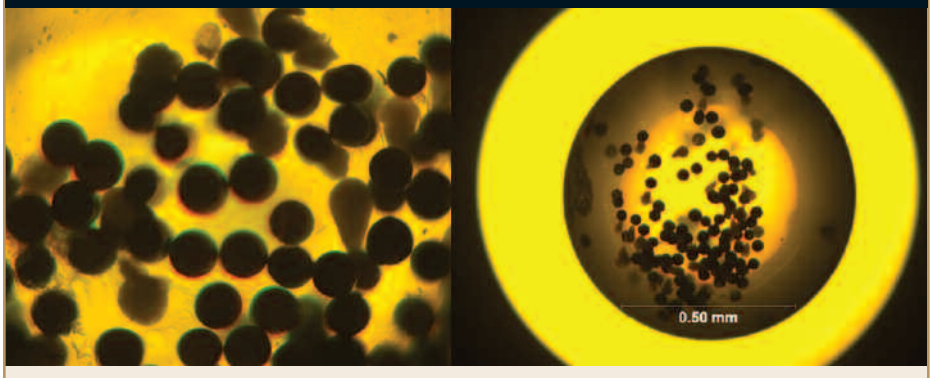
Hydrocapsule Encapsulation Machine (HEM) utilizing a liquid-liquid co-extrusion nozzle system in conjunction with a UV photo-chemical exposure chamber.

FIGURE 4



Various-size pictures (A through D) of a 2-mm Hydrocapsule containing live beneficial nematodes (*Steinernema feltiae*) at a concentration of 2,000 AU/ml in water-sucrose, which was encapsulated using an oxygen-permeable silicone containing cross-linked polymer.

FIGURE 5



A 1.5-mm water-filled Hydrocapsule with suspended *Artemia salina* cyst eggs inside

average diameter of approximately 3 mm were obtained. A sample of the encapsulated material was subsequently opened and cultured on agar in a Petri dish. After several days, extensive colonization of the Petri dish by BT was observed and verified.

Additional development was done encapsulating various biological components, such as animal blood products and tissue. To demonstrate the ability of larger particles to pass through the co-extrusion nozzles, a solution of *Artemia salina* (brine shrimp eggs) was made and successfully encapsulated (Figures 1 & 5). Utilization of pH-sensitive polymer formulations for coating and delivery of additional entomopathogens (such as viruses and fungi) have shown promising results in initial testing by government and academic laboratories and are currently proprietary.

FUTURE PHARMACEUTICAL APPLICATIONS

The use of this technology has much broader application potential in the fields of veterinary and human medical and pharmaceutical science than originally developed. Currently, new investigations are being conducted for using Hydrocapsules to deliver essential nutrients, drugs, and vaccines to farm-reared fish in large-scale aquaculture.

The unique ability of Hydrocapsules to encapsulate aqueous solutions also allows its use for delivering active ingredients in an aquatic environment. Methods of release currently being employed are based on pH-reactive coatings to allow the capsule to remain intact in water (pH 6 to 8) until ingested, and then pass through the stomach region of a fish, where the stomach acid causes a triggering of the polymer coating to begin breaking down over a predetermine time interval (based on coating thickness and formulation chemistry) and ultimately deliver its contents into the lower digestive tract of a fish. These types of reactions can be acid or alkali triggered. The formulations and mechanisms currently under development for aquaculture drug delivery have direct application to human and other animal pharma.

Additional medical/pharmaceutical applications include the ability to deliver beneficial organisms, tissues, cells, and bacteria. There is the potential need to replenish beneficial bacteria in the stomach and mouth after patient exposure to long-term treatments with antibiotics after surgical or dental procedures or after serious infections. The ability of delivering aqueous-stored anti-viral agents, antimicrobial, or aqueous-based anti-cancer treatments through oral ingestion by animals and humans is possible. There is also the possible use of delivering these same agents in combination with a topical ointment or external treatment application in which the capsules can be mechanically ruptured by direct application or rubbing of an infected area. The Hydrocapsule process allows for the encapsulation of many such agents for any of these applications and others, without the use of direct heat, extreme pressures, or solvent processes that could degrade these agents or volatile compounds or cause the breakdown or denaturing of proteins, amino acids, or lipids.

ACKNOWLEDGEMENTS

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Scientist with the USDA-ARS, CMAVE for his entomological expertise and scientific consultation during the initial development phases of the Hydrocapsule technology; David M. Thirlwell, IT Project Manager at ARS for his technical support in creating all graphics and photo images used for this paper; and Dr. Charles F. Cleland, Program Director at the USDA/CSREES SBIR Program Office for his and the USDA's support in the Phase I and II development of this technology.

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BIOGRAPHIES

Mr. Ara Manukian is the current CEO of ARS, inc. and has served as the Director of Engineering for the past 12 years, and has been responsible for management of all engineering projects for the company. Mr. Manukian, a co-pi and co-inventor of the Hydrocapsule technology, is a systems design engineer specializing in the development of electronic instrumentation and PLC-based control systems, specializing in electrical, mechanical systems interfacing and fluid flow, pressure, and temperature control. He has been responsible for over 500 engineering contract projects during the past 12 years for several academic, government, military, and private industry laboratories, working on projects ranging from design of avionic systems, space-flight hardware, analytical instruments, material processing, and chemical plant reactors. He has co-authored 20 scientific papers and several technical articles, contributed to 4 books, and has 4 US Patents. Previously, Mr. Manukian worked for 5 years as a systems engineer at the USDA-ARS, CMAVE laboratory in Gainesville, FL, in the Chemistry Research Group. In that position, he was responsible for the development of a wide range of automated volatile collection systems, bioassay systems, and analytical instrument and chemical analysis methods development for semio-chemical research. Mr. Manukian was a collaborating investigator on 10 research grants during that 5-year period and received 4 USDA Merit Awards for Outstanding Performance. Prior to working with the USDA, Mr. Manukian was employed as a research assistant in several positions under grants from NASA, University Space Research Association (USRA), Florida Space Grant Consortium, Florida Space Foundation, and Florida Challenger Astronaut Memorial Foundation. Research under these grants covered topics related to developing systems for growing crop plants in space and mathematical modeling of dynamic control systems used in a spaced-based Closed Environmental Life Support System (CELSS).

Dr. William Toreki III is a Senior Research Polymer Chemist with ARS, inc. and was a co-principle investigator and co-inventor of the Hydrocapsule technology development from 1996-2000. Dr. Toreki has worked with ARS since 1996 and was key to the formulation chemistry development for Hydrocapsules and is currently consulting with ARS on several polymer-chemistry related new product applications. Dr. Toreki is currently employed as the Chief Polymer Chemist for Quick-Med Technologies, another company also based in Gainesville, FL, which develops polymer-based systems for advanced wound care, cosmetic, medical, and military markets. Dr. Toreki has extensive research experience in various applications of polymer and silicone chemistry and has been recently focused on incorporating biologically active compounds and antimicrobial agents into various polymer systems and cellulose fibers for entomological, agricultural, biomedical, and wound-care research. He has been involved with microencapsulation, biomaterials research, and polymer fiber development for over 20 years and previously worked as a materials research scientist with the biomaterials research group in the Dept. of Material Science and Engineering at the University of Florida in addition to being a court-qualified expert witness in the field of polymer and silicone chemistry in several states. Dr. Toreki has additionally consulted to numerous companies in these same fields during the past 15 years, and has been involved in over 100 new product development projects and currently has 11 issued US Patents and 9 Patents pending, in addition to co-authoring over 20 publications. He has received an Outstanding Service Merit Award from ARS, as well as received the DuPont Excellence in Teaching Award.

On The Rise

5 Drug Delivery Companies You Should Know About

By: Cindy H. Dubin, Contributor

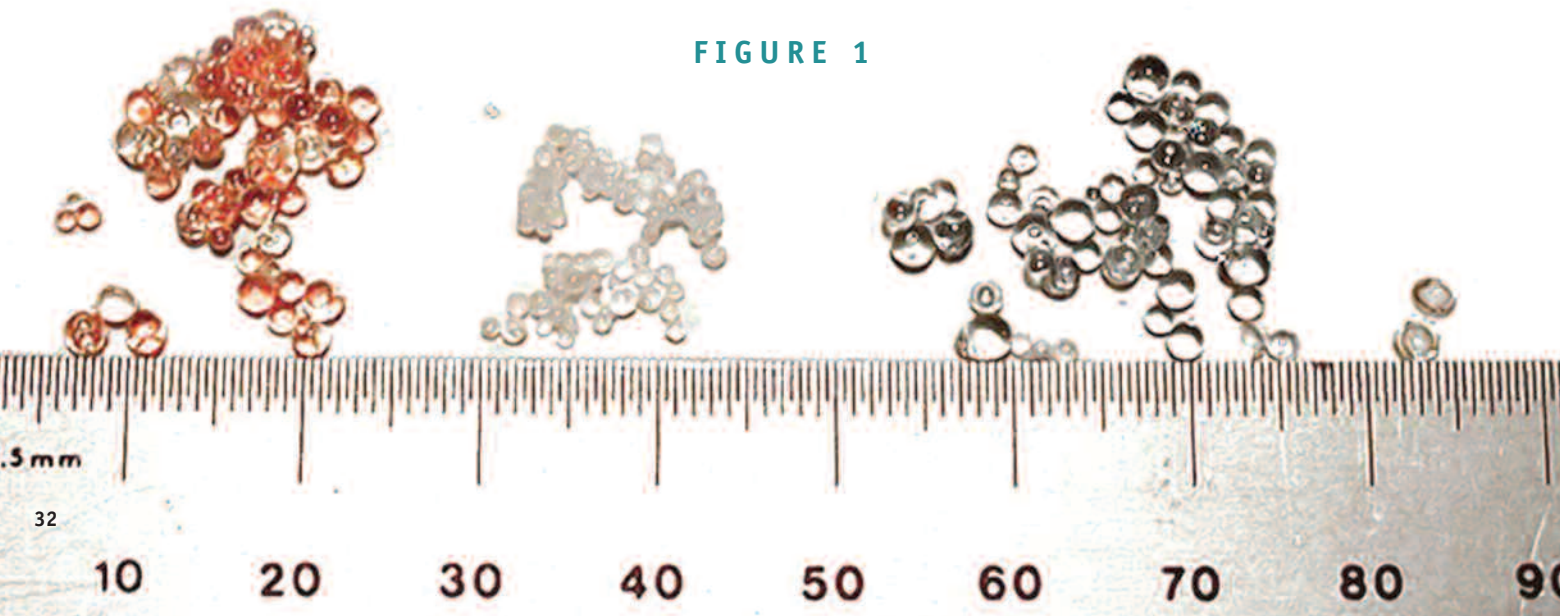
Drug delivery companies are thinking outside the box when it comes to patient compliance, dosing regimens, and methods of administration. But many of these companies are not well known by potential pharma and biotech partners, nor are they common names among their drug delivery brethren. This exclusive to *Drug Delivery Technology* magazine gathers some of these lesser-known, but worth knowing, innovators to find out more about their technologies and how they are meeting some unmet needs in the market. The companies include Analytical Research Systems, Inc., Camurus, Delcath Systems, Galenix, and IntelGenx Technologies Corp.

ANALYTICAL RESEARCH SYSTEMS, INC. — DELIVERING WATER-BASED DRUGS

Incorporated in 1994, ARS was formed to produce scientific instruments for research in both the private sector and government agencies, particularly in the field of chemical and biochemical applications. The second year the company was in business, it responded to the US Department of Agriculture's call for encapsulating a nutritional supplement (aqueous solution) for beneficial insects used in mass rearing. Many gel-based systems cannot handle more than 20% water content, explains Ara Manukian, President of ARS. The government saw beneficial insects, their mass production, and release as one method to reduce the use of harmful pesticides. ARS submitted its proposal and subsequently was awarded an SBIR Phase I and II contract. This began the company's development of the Hydrocapsule® technology (Figure 1), funded through the USDA's SBIR program. Hydrocapsules are discrete capsule(s) or microcapsule(s), of any size, shape, composition, and color that have a polymeric outer coating (shell or membrane) that surrounds an inner liquid mixture having 10% to 100% water content. The capsules are typically round and range in size from 100 microns to 2 centimeters in diameter, and are currently made between 2 to 6 millimeters. The polymeric coating or outer shell/membrane of a Hydrocapsule is made up of UV-initiated, cross-linked polymers (several of which are FDA approved) and are specifically formulated for each particular application.

The Hydrocapsule technology has been under

FIGURE 1



development since 1996 and was first used in commercial application in 2000. There are many possible Field(s)-of-Use for the technology. Some are being evaluated by ARS with other collaborating companies.

"We recognized that feeding bugs is a small market and that the technology could be used to deliver biologically active organisms, oral vaccines, and anything else that needs to be in an aqueous solution," says Mr. Manukian. "Just this year, we moved from encapsulating nutritional diets for beneficial insects to delivering entomo-pathogens and semiochemicals, and now we are getting into pharma. Several major players have showed significant and positive interest in the past 10 months."

Most of the pharma applications are for delivering traditional aqueous-based drugs for veterinary applications, but Mr. Manukian believes the ultimate goal is human drug delivery. He says: "Veterinary pharma is easier to work in from a regulatory standpoint, but we want traditional big pharma to know that we have this Hydrocapsule technology and that the possibilities of what we can do are virtually unlimited."

CAMURUS ENABLES BETTER BIOTECH DELIVERY

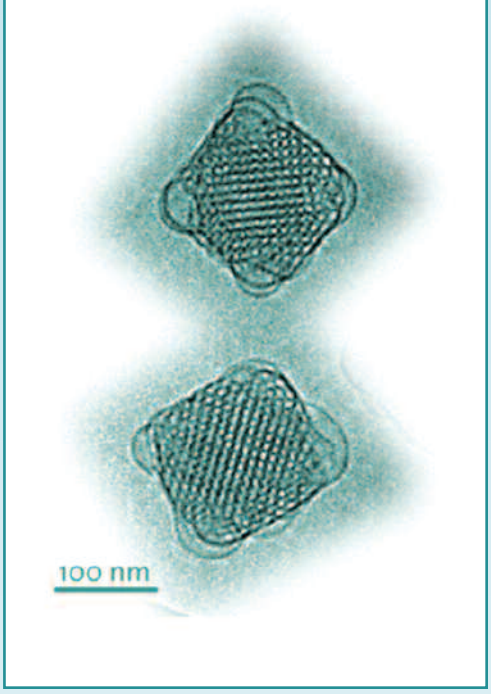
Lund, Sweden-based Camurus specializes in the development of pharmaceuticals based on advanced and effective drug delivery solutions that optimize the bioavailability and therapeutic performance of a range of difficult substances, including peptides, proteins, and insoluble small molecules. The company's nanoscale delivery technologies are used to improve existing products as well as to facilitate the creation of new therapeutics for unmet medical needs where traditional approaches have proven unsatisfactory. According to Fredrik Tiberg, PhD, CEO of Camurus, the company provides an enabling technology that helps ensure greater patient compliance. Its pipeline of drug products, both in-house and in cooperation with selected pharmaceutical and biotech partners, covers therapeutic areas in cancer, pain, infection, CNS, and metabolic disease.

Founded in 1991 by leading scientists in physical, biophysical, and food chemistry with expertise in lipid-phase structures, they recognized the drug delivery potential of lyotropic liquid crystal (LC) structures, such as the Cubosome® nanoparticle (Figure 2). The first drug product based on LC delivery systems to reach the market using the special properties of liquid crystal phase structures was Elyzol® Dental Gel. This was introduced on the market in 1993 by Dumex A/S on a license from Camurus and is now sold by Colgate® Oral Pharmaceuticals.

Camurus remained an idea-based company until 2002, when it changed its business strategy, explains Dr. Tiberg. "We started to advance our in-house product developments, partly to drive and take charge of our own technology development. So, we built up our safety documents and proof-of-principles, and validated our platform technology, FluidCrystal®. This has gotten us very far," he says.

Four years later, one product is undergoing clinical Phase IIB trials and is about to enter Phase III. Two long-acting peptide products are in clinical development, and two others are moving into the clinic. Camurus has more than 10 ongoing research collaborations with pharmaceutical partners, four of which are top 10 manufacturers.

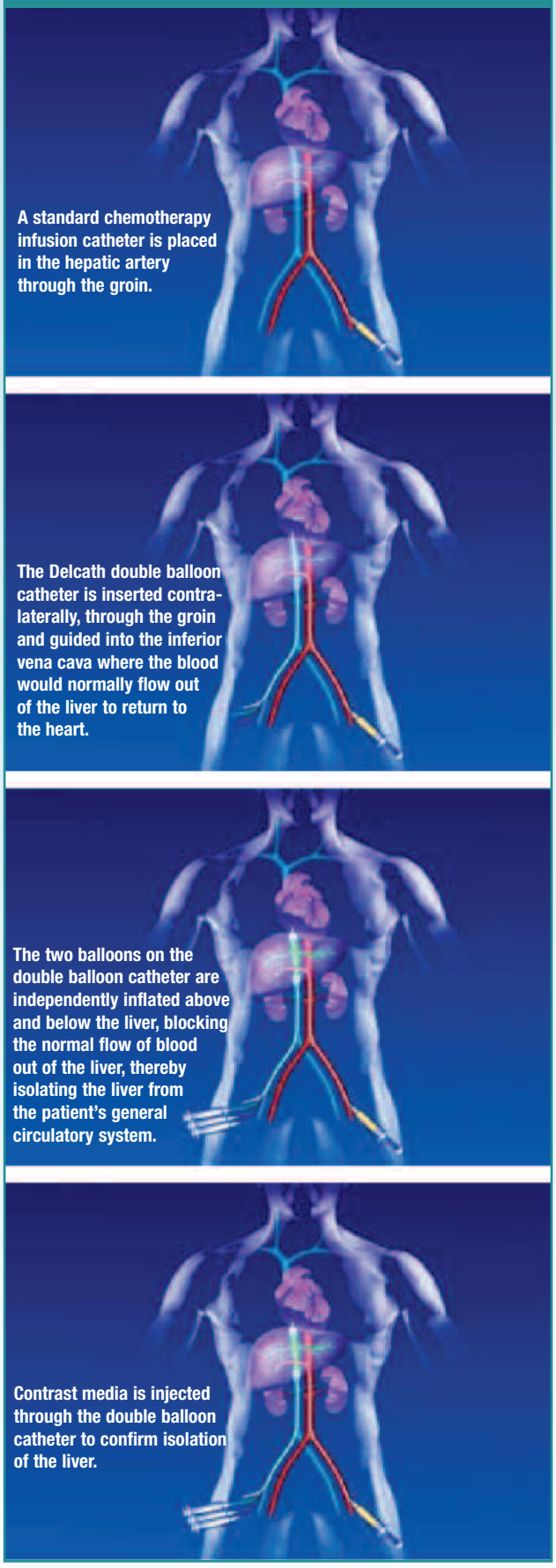
FIGURE 2



"Seventy percent of our development pipeline is biotech, and 30% is small molecule," explains Dr. Tiberg. "All of the products exploit liquid crystalline materials or part of liquid crystals."

Camurus' FluidCrystal nanoscale matrices form protective "cages" around delicate therapeutic molecules. Due to the coexistence of hydrophilic and hydrophobic domains, these structures are able to incorporate a range of drug substances from small lipophilic molecules to proteins. These structures are created *in vivo* and are used to control the release of a substance, enhance solubility, and/or to achieve bioadhesion. Camurus' FluidCrystal injectable depot is one

FIGURE 3 - PART 1



example of where sustained release performance is combined with simple administration, says Dr. Tiberg. The product is presented as a liquid, compatible with standard prefilled syringes, which upon injection into subcutaneous or intramuscular tissue, transforms into a liquid crystalline gel from which the drug compound is released over a time range, tunable from days to months. Other drug products based on liquid crystals are presented as intravenous or subcutaneous injectable solutions and gels.

According to Dr. Tiberg, the market potential of Camurus products exceeds $10 billion. "Our delivery technologies represent effective solutions to the current challenges of facilitating convenient administration and effective delivery of biotech drug products and improving patient compliance," he says.

DELCATH SYSTEMS TARGETS LIVER CANCER

Delcath Systems, Inc. is a developmental-stage drug delivery company with a percutaneous perfusion technology for organ- and region-specific delivery of ultra-high doses of chemotherapeutic agents. By isolating a specific region of the body to be treated, the Delcath System allows for the targeted delivery of chemotherapeutic and therapeutic agents in much higher dosing than otherwise feasible, thereby improving therapeutic benefit while minimizing systemic toxicity. The Delcath System, percutaneous hepatic perfusion (PHP), is in a pivotal Phase III trial at the National Cancer Institute (NCI) — having received Fast Track designation from FDA — and delivers several times the FDA-approved dosage of the chemotherapeutic agent melphalan for the treatment of metastatic melanoma in the liver. The NCI is also currently enrolling patients in a Phase II trial using the Delcath System for the treatment of primary liver cancer and metastatic hepatic malignancies from neuroendocrine cancers and adenocarcinomas. The Phase III trial has just recently been approved to expand to other leading cancer centers.

The Delcath System allows for the targeted delivery of the high-dose chemotherapy to the liver with the subsequent removal of the drug from the blood via filtration prior to returning the drug-laden blood coming out of the liver to the patient's circulatory system (Figure 3). The filtration extracts the drug from the blood, protecting other parts of the body from the harmful side effects of

chemotherapy, and allows for much higher doses of drug to be delivered to the targeted liver, potentially improving efficacy.

The Delcath System is a non-surgical and repeatable procedure, having been administered up to 10 times to a patient. "What sets Delcath apart from other treatments for liver cancer is the ability to treat the entire tumor-burdened organ with high-dose chemotherapy," says Richard Taney, President and CEO. Mr. Taney further comments on the growing acceptance of regional and adjuvant therapies, pointing out that, "We envision the Delcath System becoming the first line method for treating liver cancer, as well as becoming the standard follow-up procedure to resection, radioactive microsphere technology, radio frequency ablation, and chemoembolization, creating advanced and effective adjuvant therapy for liver cancer."

GALENIX — FROM CSO TO DDS

Galenix was set up in 1993 in Bordeaux University. The French company started its business mainly by providing contract pharmaceutical development services to the health industry. The cornerstone of Galenix activities is formulation. After 1999, the company's own research projects became more important than contract development. In 2006, a banner year in the company's history, it forged relations with the Bristol-Myers Squibb Pharmaceutical Research Institute. With these facilities, Galenix broadened its portfolio of services, especially with the ability to produce European and US FDA GMP clinical batches, explains Jérôme Besse, Scientific Department, Director, CEO, and Chairman.

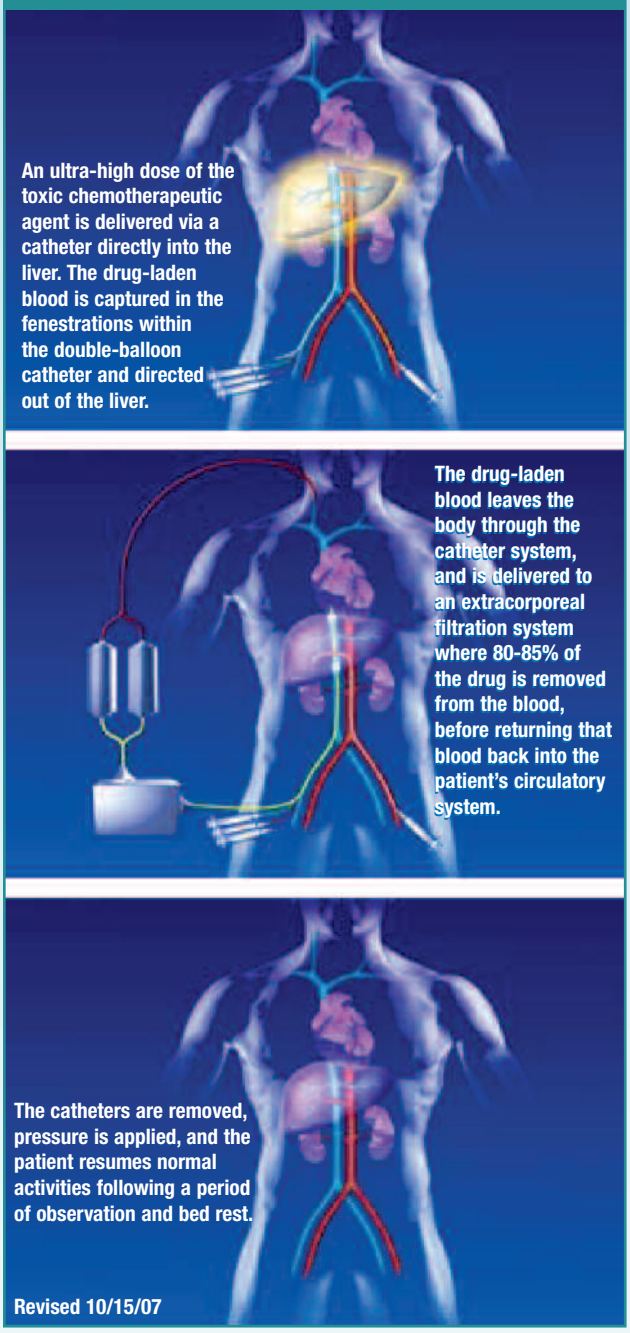
MICROGIX® (Figure 4) is the company's technology to improve solubility and/or bioavailability of poorly soluble and/or bioavailable API.

MICROGIX is a dispersed liquid system adsorbed on an inert powder support for oral route. It can be formulated in a sachet, capsule, tablet, or spray powder. According to Mr. Besse, MICROGIX can improve the bioavailability and/or solubility of poorly bioavailable and/or soluble APIs (BCS class II, III, and IV); protect sensitive APIs, such as biologicals, and pH-sensitive APIs; and help in the development of modified and long-acting release products.

"MICROGIX is for mature APIs or NCEs or very sensitive biologicals in the BCS classification II, III, or IV if the laboratory wants to develop a suprabioavailable solid dosage form," adds Mr. Besse.

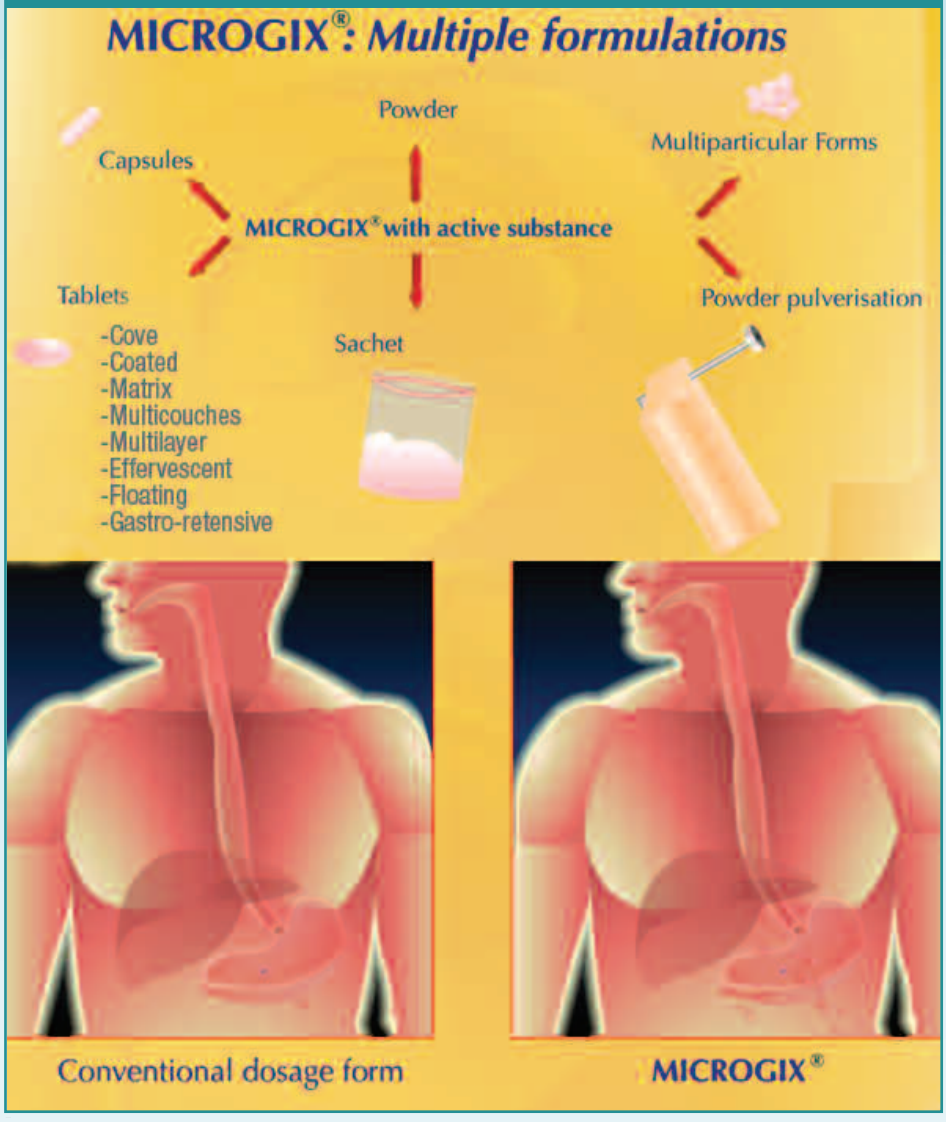
Galenix is currently developing more than 14 different APIs for life cycle management, NCEs, or biologicals product development, and expects to launch two of them in Q3 2008.

FIGURE 3 - PART 2



Mr. Besse indicates his long-term objectives for Galenix from a drug delivery perspective include combining APIs with Galenix DDS portfolios through its own drug product development programs or contract services business activities in an effort to license the DDS and product in the best financial conditions to guarantee higher revenues; and developing other DDS dedicated to biological oral administration.

FIGURE 4



INTELGENX TECHNOLOGIES CORP. — RELIABLE & AFFORDABLE DELIVERY

IntelGenx is a drug delivery company focused on the development of oral controlled-release products as well as rapidly disintegrating mucosal delivery systems. Founded as a Canadian corporation in 2003, the company remained fairly quiet until late October 2005. It closed on a seed round of funding in May 2006, became public through a reverse merger, and changed its name to its current incarnation.

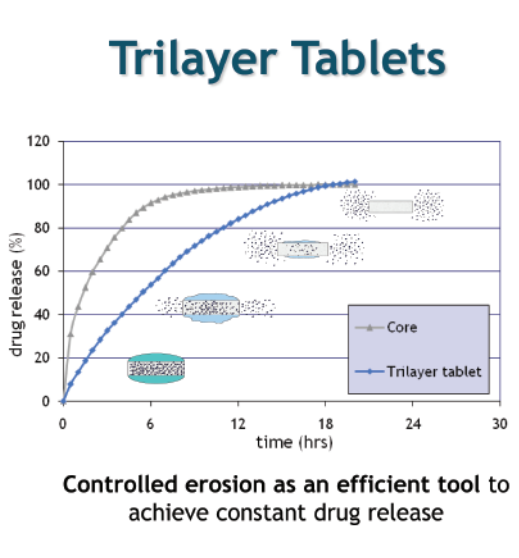
"Our goal was to become a cost-efficient developer of novel oral drug delivery technology," says Horst Zerbe, PhD, President and CEO.

And that is how the firm markets itself and its two platform technologies; one is a layered tablet oral controlled-release technology, and the other is an instantly disintegrated oral film. "Both have proven to be viable enough to base our development on, and we have developed a viable drug delivery unit around those platforms," he says.

The company's R&D pipeline includes products for the treatment of osteoarthritis pain management, hypertension, and smoking cessation. The company uses its multiple layer delivery system to provide zero-order release of active drugs in the gastro-intestinal tract. The Tri-Layer platform technology (Figure 5) represents a new generation of controlled-release layered tablets to modulate the release of active compounds. The technology is based on a Tri-Layer tablet with an active core layer and two erodible cover layers. The release of the active from the core matrix initially occurs in a first-order fashion. As the erodible layers start to disintegrate, the permeation of the active ingredient through the cover layers increases. The Tri-Layer tablet can produce quasi-linear (zero-order) kinetics for releasing a chemical compound over a desired period. The erosion rate of the cover layers can be customized according to the physico-chemical properties of the active drug. The company's lead product is INT0001/2004, a once-daily formulation of a hypertensive medication.

"Up until the point when we developed our platform, many of the significant oral CR products for once-daily administration were based on osmotic technology," explains Dr. Zerbe. "That technology has some limitations, such as solubility of the active in water, and only a limited number of drug candidates can be formulated in that platform. Additionally, osmotic tablets are expensive to manufacture, which can be issue for genericized products. Our objective was to provide a system that exhibited the same characteristics with respect to drug release as those

FIGURE 5



osmotic systems, yet making it applicable to more compounds, and do so more cost effectively."

The Quick Release Wafer technology is made up of a thin (25 to 35 microns) polymeric film comprised of USP components that are safe and approved by the FDA for use in food, pharmaceutical, and cosmetic products. Derived from the edible film technology used for breath strips and initially developed for the instant delivery of savory flavors to food substrates, the Instant Delivery Film has distinct advantages over existing fast-dissolving oral tablets, which Dr. Zerbe believes make it the application system of choice for indications requiring rapid onset of action like migraine, motion sickness, and nausea.

The Quick Release Wafer consists of a blend of film-forming polymers with self-emulsifying modified starches that ensure instant disintegration of the film on the buccal mucosa and allow for the formulation of lipophilic components into the film base without using surfactants. A unique feature of the film is its ability to retain volatile components, like nicotine or nitroglycerine, which might otherwise evaporate during the drying process.

"We are at the forefront of this technology for prescription medications," says Dr. Zerbe. "The development of this platform was driven by indications that required the rapid onset of action, like migraines. Our expectation is that with film, we are able to prevent these types of attacks from even manifesting themselves; a real therapeutic breakthrough."

Dr. Zerbe points out that IntelGenx delivery platforms involve proven manufacturing technology and FDA-approved excipients, and wants the company to become known for providing reliable and affordable technology. "Our technologies are down-to-earth and proven, which means that the probability of bringing our partners' drugs to market is close to 100%," he says.

BIOGRAPHY

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

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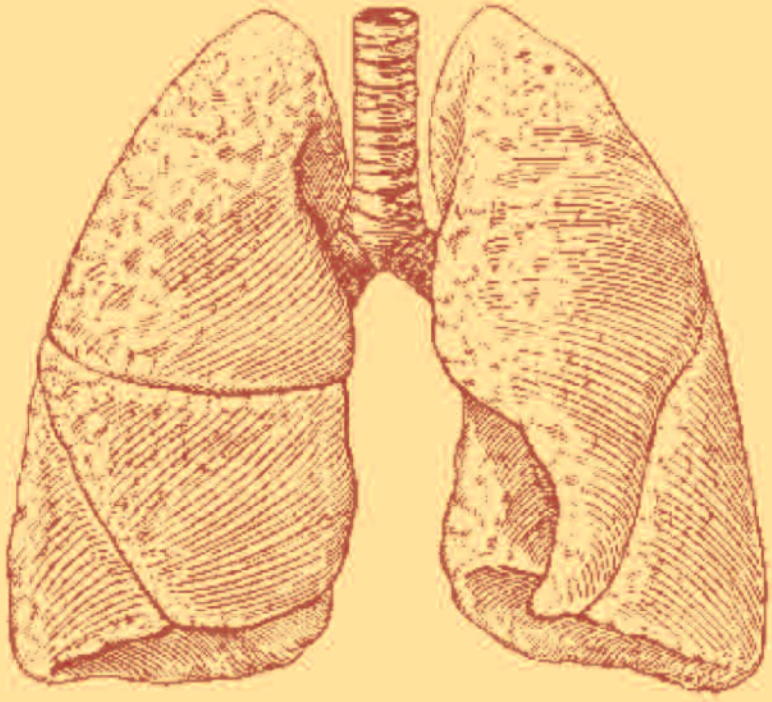

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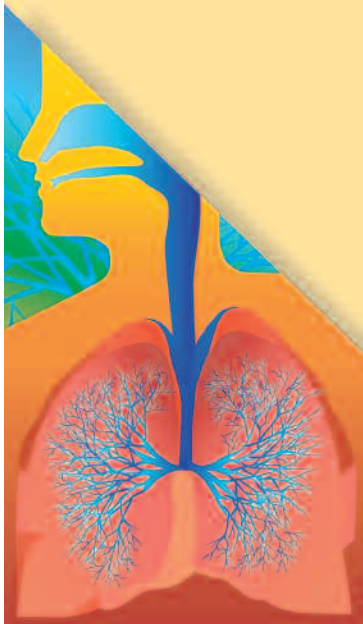

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AEROSOLIZATION ANALYSIS

Unlocking the Secrets of the Dry Powder Inhaler Plume

By: Paul Kippax and David Morton

INTRODUCTION

Developing new inhalation technologies is a significant goal for the pharmaceutical industry. Demand for the treatment of respiratory diseases is increasing, and the advantages of systemic drug delivery via the pulmonary route are becoming progressively more attractive. Nebulizers, metered dose inhalers (MDIs), and dry powder inhalers (DPIs) are all commonly used delivery platforms, with the latter currently receiving the most attention. It is argued that DPIs avoid the problems associated with propellants, are simple to use, have a greater dose range than other devices, and provide advantages when formulating fragile molecules. Producing DPIs that consistently deliver the required dose of active ingredient to the lung is, however, challenging.

Effective DPI design rests on optimizing both the formulation and the delivery device, and these should be intelligently and specifically matched for any given application. Such consideration must include the site of action of the drug in the lung as well as the nature and anatomy of the patient. Particle size and velocity determine aerosol transport and deposition; for example, whether the drug is drawn deeply into the lung or upper airways or is swallowed from the throat. Consequently, detailed spray plume analysis, including size measurement of constituent particles, is a major part of the design process. In this article, we describe the technique of laser diffraction-based particle size analysis for the study of DPI sprays, demonstrating the insight it delivers into formulation and device behavior. Included is an examination of the factors influencing powder dispersion and a case study that illustrates how different excipients can improve the performance of a formulation.

INHALATION: A GROWING ROUTE OF DELIVERY

While the inhalation route is an obvious choice for the treatment of respiratory diseases, such as chronic obstructive pulmonary disease (COPD) and asthma, the recent approval of Exubera, an inhaled insulin treatment for diabetes, demonstrates its wider potential.

Inhalation, and subsequent absorption in the lung, can result in substantially more rapid onset of action compared to oral delivery methods. It also avoids the possibility of first-pass metabolism in the gastrointestinal tract. From a patient perspective, inhalers can be easy to use and for many people, their non-invasive nature makes them more acceptable than intravenous alternatives. Commercial drivers for continued development are strong because the technology affords options for product differentiation and extension via a changed delivery platform.

DPIs are attractive because the delivery process is actuated by an intake of breath, circumventing any issues of coordination. With no propellant present, they avoid environmental concerns and do not suffer the turbulent oral deposition and freezing effects associated with more traditional aerosol devices (such as MDIs). Their dry state allows

FIGURE 1

FPFs Produced Using Three Different Commercially Available Inhalers With Two Different Drugs - Salbutamol & Budesonide

Drug	Turbuhaler	RotaHaler
Salbutamol	14%	6%
Budesonide	63%	14%

FIGURE 2

FPF Data for the Untreated & Coated Lactose Formulations

Test Powders	Monohaler FPF (% < ~6 µm)
Formulation 1	32
Formulation 2	35
Formulation 3	73

formulation with reduced stability problems for fragile molecules, such as proteins, rDNA, and peptides. A significant challenge with DPIs, however, is to ensure that the energy provided by inhalation consistently disperses the active drug to a suitable respirable size (typically less than 5 microns).

FORMULATING DRY POWDERS FOR INHALATION

Forces of adhesion (attraction between dissimilar surfaces) and cohesion (attraction between like molecules) dominate the behavior of very fine powders, especially when the particle size is below 10 microns. Capillary, van der Waals, and electrostatic forces are all important at this reduced particle size, with van der Waals dominant under most "normal" dry conditions. Within a DPI system, it is important to consider carefully the cohesive forces between drug particles, the adhesive forces between device and drug, and the carrier/excipient and drug.[1]

Carriers of relatively large particle size are often used to improve the flow characteristics of a DPI formulation. These facilitate not only filling and metering but also emptying, and enhance powder stability. The choice of excipients approved for this application is limited, with lactose used most commonly. Ideally, drug-carrier interactions ensure that the drug adheres to the excipient up until the DPI is actuated. Then the inspiratory breath should provide sufficient energy to detach the active drug from the carrier for inhalation into the lung. To achieve this, the balance of the interparticulate forces is critically important.

The development of carrier-free

FIGURE 3

Particle Size as a Function of Flow Rate for Unprocessed Lactose (Formulation No. 1)

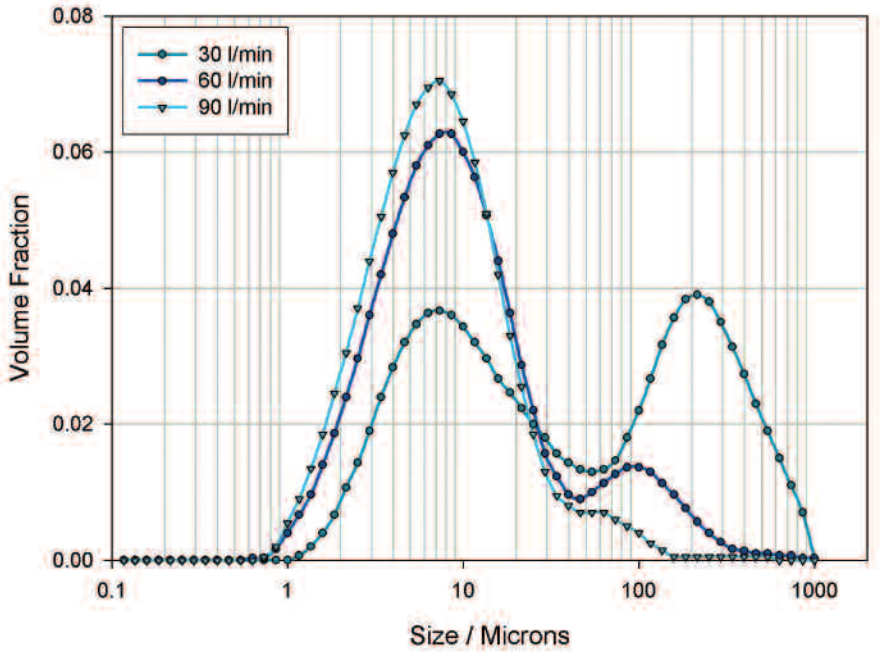


FIGURE 4

Aerosol Volume Concentration as a Function of Time for Unprocessed Lactose (Formulation No. 1)

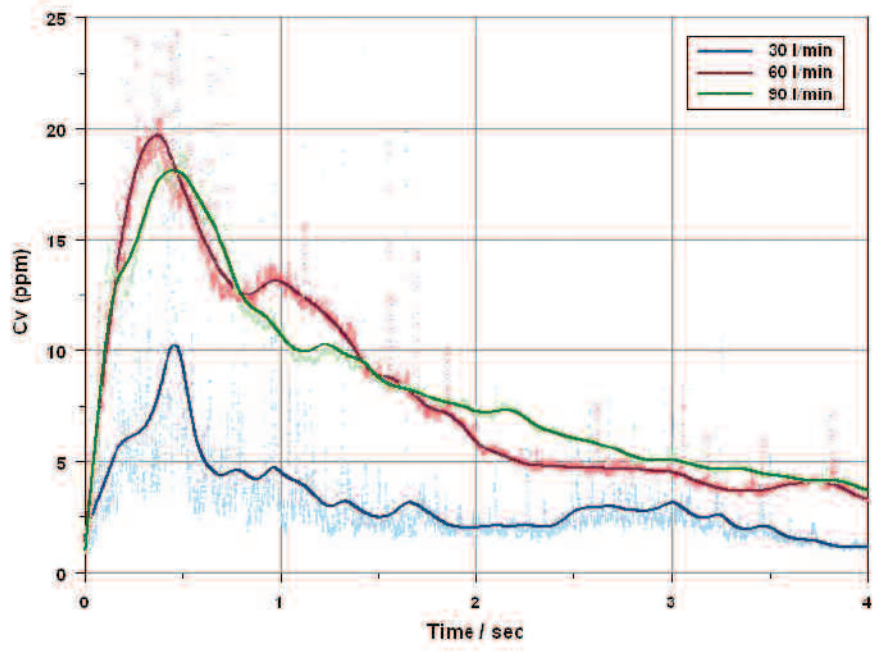


FIGURE 5

Particle Size as a Function of Flow Rate for Lactose Blended With Magnesium Stearate

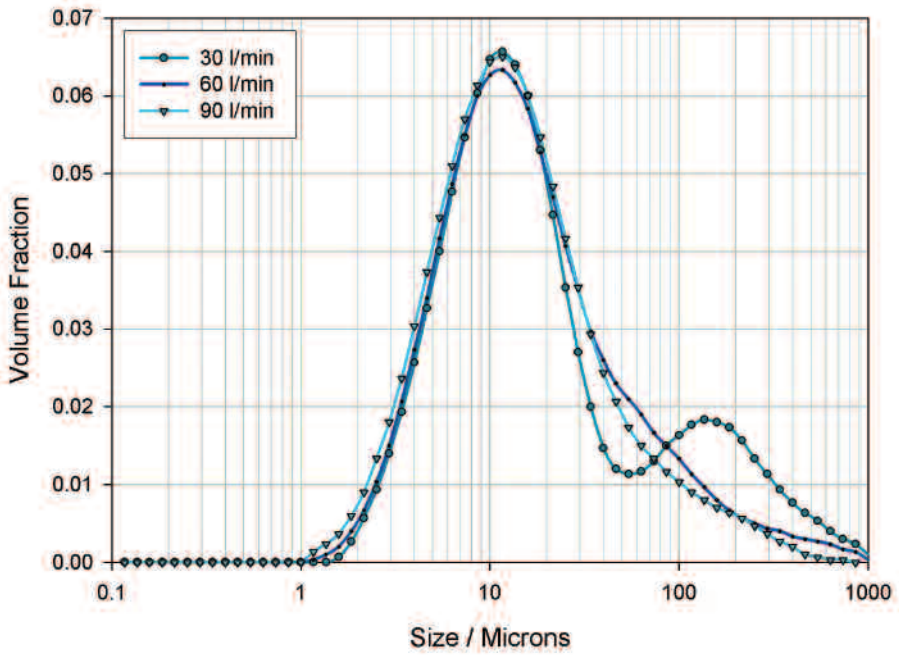
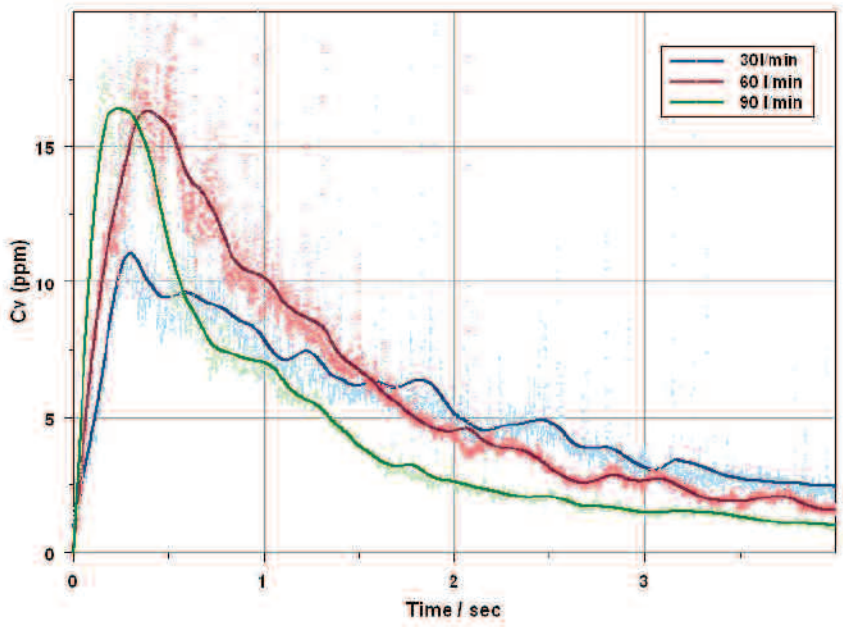


FIGURE 6

Aerosol Volume Concentration as a Function of Time for Lactose Blended With Magnesium Stearate



formulations is of significant interest, in particular for relatively high-dose applications or those where there are chemical interactions between carrier and active ingredient, or for patients with carrier intolerance (a specific problem with lactose). However, these systems return the formulator to the problems associated with highly cohesive fine particles: poor flow during capsule filling and poor aerosolization behavior resulting from the difficulties associated with de-agglomeration. Thus, it is essential to understand the factors that influence performance and the ways in which they can be manipulated.

RELATING PERFORMANCE TO POWDER PROPERTIES

The fraction of an inhaled dose that (because of its particle size) will enter the lung is commonly referred to as the fine particle fraction (FPF). A simplistic view would predict a strong link between FPF and the strength of cohesive/adhesive forces, with FPF increasing as interparticle forces decrease. The development of screening methods has, to some extent, been based on this hypothesis. Techniques are therefore available for the prediction of FPF from measurements of surface activity and/or powder flowability.

Unfortunately, the dispersion behavior of DPIs is less easily rationalized. Consequently, these techniques must be used with some care, as the following examples illustrate.

Figure 1 shows the FPF produced when two different drugs, salbutamol and budesonide, are used in different commercially available DPIs. Investigations were reported to show that the surface

energy of micronized budesonide was five times higher than that of salbutamol sulphate, but that with each inhaler, budesonide delivered better performance - a higher FPF.[1]

This study demonstrates the dangers of trying to relate DPI performance to surface energy measurements alone. It further suggests that the mechanism by which aerosolization is achieved can be a key, sometimes overriding, factor. For instance, the achieved inspiration effort (pressure drop), which determines energy input into the system, and the entrainment and transport behavior of the powder within the device, may play a part. In particular, such studies have concluded that the residence time of large agglomerates in areas of high shear may be critical to the extent of dispersion. Changes in residence time are often manifested as changes in plume size and density. This highlights the importance of studying the formulation and device in combination, and the value of tools that can elucidate entrainment and agglomerate behavior.

LASER DIFFRACTION PARTICLE SIZE ANALYSIS

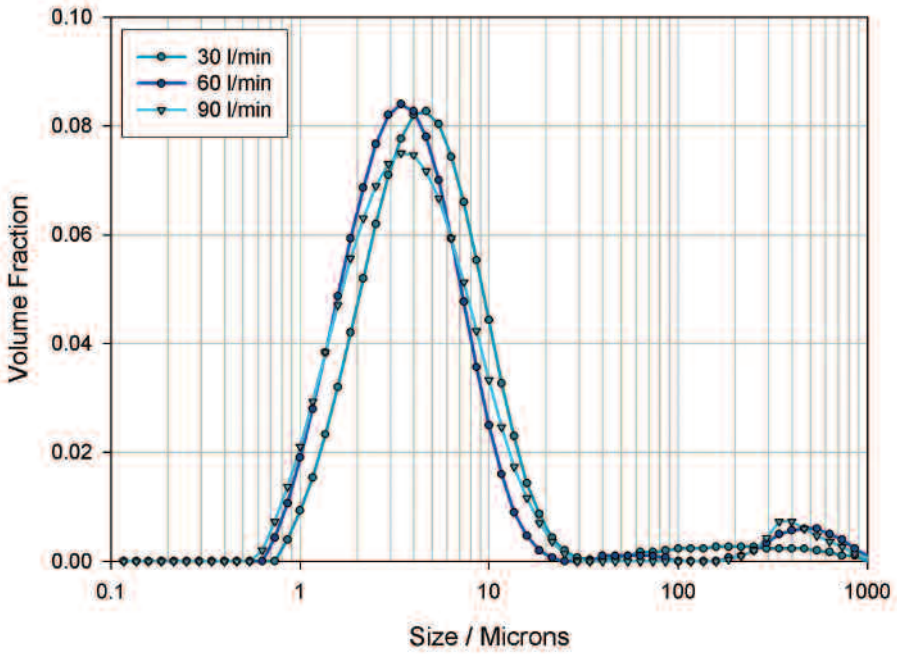
One of the most direct ways of monitoring the impact of different factors on dispersion is to measure, in real-time, the size of particles produced during discharge of the DPI, including size measurement as a function of plume duration. This requires an analytical method with a measurement rate fast enough to capture the detail of a spray event that may be complete in less than a second. Laser diffraction can achieve this and has additional advantages that make it extremely suitable for studying DPI plumes.

With laser diffraction, particle size is determined by measuring the intensity of light diffracted at different angles as monochromatic light penetrates a spray plume. Light is scattered by particles or droplets in a way that correlates directly with particle size; this is back-calculated from the measured diffraction pattern. The best instruments have measurement rates as high as 10 kHz (one measurement every 0.1 millisecond) enabling capture of the fine detail of a spray event, and a wide dynamic range that permits simultaneous measurement of agglomerates and well-dispersed particles. Measured particle size is independent of air flow rate, which can therefore be varied to mimic breathing profiles.

An important characteristic of laser diffraction is the real-time nature of the measurement. It is a rapid, high throughput technique capable of individually analyzing the particle size and concentration profiles associated with hundreds of device actuations in a single day. This contrasts with cascade impaction, a well-established method for the analysis of pharmaceutical sprays, but one that is notoriously slow, and time and resource consuming. Unlike cascade impaction, however, laser diffraction is not drug specific; it generates size but not compositional information. With appropriate usage, these two techniques can become complementary during DPI development, provided that adequate cross-validation is ensured.[2]

FIGURE 7

Particle Size as a Function of Flow Rate for Magnesium Stearate Coated Lactose (Mechanofusion Process - Formulation No. 3)

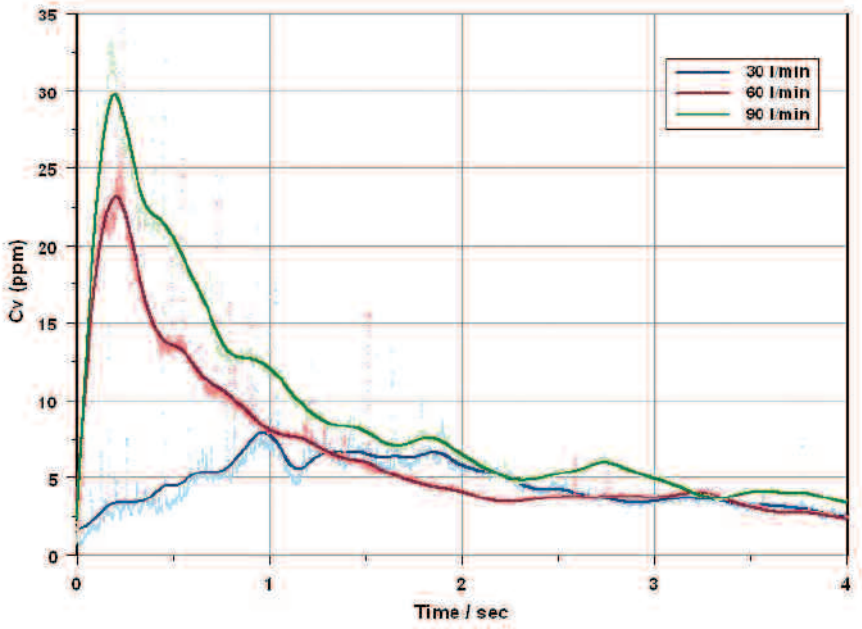


USING COATINGS TO IMPROVE DISPERSION

Having outlined the nature of the challenge and the tools available to study possible solutions, it is appropriate to consider how powders for inhalation can be engineered to behave in the required way.

FIGURE 8

Aerosol Volume Concentration as a Function of Time for Magnesium Stearate Coated Lactose (Mechanofusion Process - Formulation No. 3)



Here we examine the impact of coating additives on powder dispersion, simultaneously demonstrating the practical relevance of data generated using a laser diffraction analyzer, in this case a Spraytec from Malvern Instruments.

In a series of studies, the dispersion characteristics of three different lactose samples were examined using a twin stage impinger (TSI) and laser diffraction analysis.[3,4] The first formulation (No. 1) contained lactose micronized to a respirable size. This micronized lactose was coated using 5% w/w of magnesium stearate in a conventional high shear mill (Grindomix, Glen Creston) to produce formulation No. 2. Finally, formulation No. 3 was produced by taking the micronized lactose and coating it with 5% w/w of magnesium stearate using a high-intensity process pioneered by Vectura Group plc.[5] This process employs a mechanofusion system (Hosokawa-Alpine) and is designed to deliver a more uniform surface coating.

Exactly 10-mg doses of each formulation were placed in capsules and delivered using the Monohaler device (Miat SpA, Italy). For the laser diffraction experiments, spray measurements were made at three different air flow rates (30, 60, and 90 L/min) at the output of a standard USP induction port (USP throat). Particle size and concentration data were collected over a period of 4 seconds for each actuation.

The FPF% data for the three formulations (Figure 2) indicated changes conferred by the coating. It suggests that coating via conventional processing gave little, if any, improvement in dispersion, but the mechanofusion process had a substantial impact. However, it is well known that TSI FPF values can be indiscriminate measures of dispersion, as no fine detail of the particle size profile is provided below the estimated nominal cut-off range.

In contrast, the laser diffraction analysis provided a significantly greater level of detail in the study of the aerosol plume generated from the three different powders.[4] Figure 3 shows the continuous particle size distribution of the plume as a function of air flow rate for formulation No. 1. At 30 L/min, large agglomerates (>50 microns) were present in significant quantity, and while higher flow rates provide improved dispersion, such larger agglomerates were still detectable at air flows of 90 L/min. Further, Figure 4 shows the aerosol volume concentration data as a function of time, allowing determination of the rate at which powder is released by the device. The results indicate that the powder was rapidly entrained with an air flow rate of 60 L/min or more, but at 30 L/min, powder release was relatively slow. This is considered to be characteristic of a cohesive powder.

Comparable results for formulation No. 2 indicated that blending with magnesium stearate did not produce a coating that eliminates dispersion problems (Figure 5). Large agglomerates (>50 microns) were observed at low flow rates (30 L/min). Although these are dispersed at higher flows, the resulting model particle size is larger than for the unprocessed lactose. This is indicative of the presence of a population of smaller agglomerates within the powder. It is proposed that these may be compacted, coated agglomerates formed during the blending process. These agglomerates, likely to be subjected to press-on forces, have become difficult to disperse further to a respirable size. It is interesting to note that the aerosol concentration data in Figure 6 show that this treatment has, however,

promoted entrainment with rapid powder release being observed at all flow rates. This is unsurprising because the proposed coated agglomerates that make up this formulation would be expected to have better flowability than a micronized powder.

Results for formulation No. 3 were distinct from the other two. The proposition here is that the increased energy input associated with the mechanofusion process ensures break-up of agglomerates during blending with magnesium stearate, leading to the coating of individual lactose particles. The resulting particles were dispersed by the inhaler to a respirable size even at low flow rates (Figure 7). There is little evidence of any agglomerates in any of the analyses, and particle size was independent of flow rate, suggesting that dispersion would be achieved regardless of the breathing profile.

The corresponding aerosol concentration data (Figure 8) show that at 60 and 90 L/min, entrainment was extremely effective, and the device was emptied more rapidly than with either of the other two formulations. However, it is interesting to note that at 30 L/min, entrainment was slower. It is proposed that the 30 L/m flow is insufficient to fluidize this powder adequately, given that it appears to be very finely divided, albeit with a reduced level of cohesion.

SUMMARY

By improving particle properties and device design, the pharmaceutical industry is creating new opportunities for the use of DPIs in response to the demands of the market. DPI design is, however, challenging. We contend that studying powder properties alone is insufficient for the development of new formulations and inhalers. Studying and understanding the dynamics of aerosolization and the impact of agglomeration and entrainment are argued to be an invaluable part of effective product development.

Laser diffraction is a high throughput screening tool of significance to the DPI developer. Capable of measuring, in real time, the spray plume produced by an inhaler, it allows detailed study of aerosolization behavior and rapid assessment of the impact of air flow rate/breathing profile on dispersion. An additional strength is its ability to simultaneously detect both dispersed and agglomerated particles. The results generated are complementary to the data from cascade impaction and can provide unique and important insight that is valuable for optimizing delivery devices and formulations.

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BIOGRAPHIES

Dr. Paul Kippax earned a degree in Chemistry and a PhD in Colloid and Interface Science, both obtained at the University of Nottingham in the UK. He joined Malvern Instruments in 1997 as an Applications Scientist and in 2002 became Product Manager for the company's Laser Diffraction Particle Size Analysis Systems. He has worked closely with the pharmaceutical industry in understanding how laser diffraction techniques can be best applied to characterizing the performance of medical devices. This has included the publication of several joint research articles relating to the optimization of drug delivery from dry powder inhalers and nasal sprays.

Dr. David Morton earned his PhD from Bristol University in the UK in Structural Chemistry. He then spent 8 years in the UK nuclear industry with AEA Technology, developing expertise in the generation and transport of aerosols. In 1997, he joined the Centre for Drug Formulation Studies, University of Bath, managing its dry powder inhaler product development programs. In 1999, this group spun out into the drug delivery company Vectura, where he was Head of Pulmonary Research, and later Head of Intellectual Property and Technology. He is currently a Senior Lecturer in Formulation Science at the Victorian College of Pharmacy, Monash University, Australia. Dr. Morton has had a major role in developing the annual *Drug Delivery to the Lung* international series of conferences on behalf of the Aerosol Society since 1997.

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Mr. Geoff Bennett
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"The future of dissolvable films lies in multiple pharmaceutical, biopharmaceutical, and medical arenas. Today, 90% of all drugs are small molecules synthesized through chemical reactions; 10 years from now, as much as 70% of drugs will be large molecules."

Adhesives Research (AR) is one of the world's leading independent developers and manufacturers of custom, high-performance pressure-sensitive adhesives, tapes, specialty coatings, films, and laminates. Founded in 1961, the company's technology and products serve the pharmaceutical, medical device, and diagnostic, industrial, electronics, pulp and paper, and brand protection markets. Adhesives Research was the first North American company in its industry to be certified for the ISO 9001 and ANSI/ASQC Q9001-1994 quality assurance standards and is certified to ISO 9001:2000 standards. Today, AR has two technical centers for design and development in Glen Rock, Pennsylvania, and Limerick, Ireland, with sales and marketing offices in Great Britain, Germany, Singapore, and China. It has several segregated GMP manufacturing facilities for the manufacture of both components and active-loaded products for the pharmaceutical industry. Drug Delivery Technology recently interviewed Geoff Bennett, President of Adhesives Research, Inc., to learn more about AR and his perspective on the drug delivery industry.

Q: Can you provide a brief overview of Adhesive Research's history?

A: Adhesives Research is one of the world's leading independent developers and manufacturers of pressure-sensitive adhesive (PSA) systems, custom-coated products, and specialty films. Three of the company's divisions develop platforms for drug delivery and brand protection of pharmaceuticals. Our Pharmaceutical group has been providing skin-friendly adhesives and laminates for transdermal and topical delivery for over 20 years. Our newer venture, ARx, LLC, offers customized drug delivery platform technologies, including custom-developed dissolvable films and adhesive platforms for oral and transdermal drug delivery and biopharmaceuticals. ARmark™ Authentication Technologies, LLC, develops covert markers for anti-counterfeiting that can be combined with custom-developed delivery systems for application directly on pharmaceutical tablets and in packaging.

In addition to the pharmaceutical industry, we also serve the medical, engineered tapes, electronics, and splicing markets. We've been in business for over 45 years, with more than 20 of those years spent servicing the pharmaceutical industry. Throughout the years, we have pioneered the use of many adhesive and coating technologies to enable the world's leading pharmaceutical, drug delivery, and consumer companies to innovate, launch products and enter new markets.

Our technologies for the pharmaceutical industry include skin-friendly pressure adhesives, electronically and ionically conductive coatings,

dissolvable films and erodable pressure-sensitive adhesives, ethanol and enhancer-tolerant coatings, ultra-clean and non-reactive adhesives, hydrogels and organogels, hybrid pressure-sensitive adhesives, molecularly imprinted polymers, and tight thickness tolerance adhesives.

Q: After more than 20-plus years in the pharmaceutical industry, what do you consider to be among the most significant advancements within drug delivery technology?

A: Twenty years ago, we became involved in the onset of numerous transdermal drug delivery patch products, a technology that changed the drug delivery industry and what it was able to offer consumers. I think we are seeing the same thing happening today with oral thin film (OTF)/quick-dissolve drug delivery formats that bring additional value and convenience to the consumer. Our drug delivery partners are asking us to formulate component materials and coatings to include their specific APIs. Dissolvable OTFs are now a proven technology for the systemic delivery of APIs and have emerged as a practical alternative to traditional OTC medicines, such as liquids, tablets, and capsules.

The next generation of dissolvable films is being designed to move beyond immediate-release oral delivery into applications such as implantable, topical, sublingual, and gastro-retentive platforms for the delivery of both small and large molecules. The recent launch of multi-drug combination products are just the beginning in advancing the application of OTF technology.

The future of dissolvable films lies in multiple pharmaceutical, biopharmaceutical, and medical arenas. Today, 90% of all drugs are small molecules synthesized through chemical reactions; 10 years from now, as much as 70% of drugs will be large molecules. As new drug delivery technologies emerge, it is critical for us to continue to provide new materials that enable the commercialization of these products for our customer partners.

Q: What is your company doing to position itself for the growing demand for innovative drug delivery systems?

A: As device and drug delivery continue to converge into integrated systems, AR continues to develop platform technologies to support the needs of its clients. As the manufacturing of active transdermal delivery systems increases in complexity, customers are looking for adhesives to go beyond bonding. For example, we are designing adhesives that promote electrical and ionic conductivity for use in device-assisted drug delivery and coatings with molecularly imprinted polymers.

Additionally, our ARx division recently opened a new state-of-the-art, 25,000-sq-ft pharmaceutical manufacturing facility designed to manufacture dissolvable film, transdermal, and buccal drug delivery systems for OTC, prescription, and biopharmaceutical products. The globally compliant facility triples ARx's manufacturing capacity and laboratory space to support the rapid growth in the industry.

Adhesives Research started handling APIs 3 years ago in a smaller, 18,000-sq-ft production area within our existing Glen Rock facility. Through careful evaluation and testing, we were able to streamline the existing manufacturing process to optimize the drying process, creating a more efficient system when we moved into the new, dual-suite facility. The current facility and evolving pipeline further support ARx's market leadership by quadrupling potential strip output to more than 1.5 billion strips per year.

Q: What role does dissolvable thin film technology play in improving drug delivery, and how does it benefit the consumer?

A: It really comes down to patient compliance. Dissolvable thin film technology provides consumers with

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a choice of delivery options for taking OTC and prescription medicines. Quick and precise dosing, convenience, and portability are among the key benefits of this new technology. Dissolvable films have proven to be very popular for the pediatric population, who usually ingest the entire thin film dose (versus liquid that can be expelled from the mouth), as well as with geriatric patients and others who have difficulty swallowing pills and for those who simply need an on-the-go form of relief. These benefits serve to increase patient compliance and have proven to be well-tolerated.

In addition to increasing compliance, another primary benefit of dissolvable film technology is the flexibility of the format. Dissolution rate, material section, and the rate of absorption can all be controlled. ARx's manufacturing capabilities provide advantages in bringing a new product or extension of an existing product to market.

Q: What do you consider to be the key reasons behind a company's decision to partner with Adhesives Research?

A: Our customers turn to us for our formulation and manufacturing expertise in the adhesives and coating industry combined with our flexibility to create a completely customized solution to meet their needs. Companies know they can turn to us when they have unmet needs in the design of critical components for their specific applications. If a company wants a cookie-cutter solution, they most likely don't want Adhesives Research.

Our customers also know that we are going to be here for them. As an independent, private company that's been in business for over 45 years, we are committed to our customers and the industries they serve. Twenty years ago, we committed to the pharmaceutical industry to help them develop transdermal patches, and we continue to stay interested and focused without compromise.

Insight is at the core of everything we do – from the development of technologies to practical applications, we turn possibilities into viable solutions by modifying or combining existing technologies (or by developing new technology), altering manufacturing processes, or modifying equipment to yield the right component.

We use a four-stage process to manage the successful custom development of pressure-sensitive adhesive systems, coatings, films, and laminates. Each project has a dedicated team (R&D, chemists, process engineers) to keep the project on schedule and assure quick response to the customer.

Q: Where do you see your company in the next decade?

A: Looking forward, I believe we will continue to maintain the focus that has sustained us for over 45 years. One of our corporate objectives is to be the most effective company in our field at partnering with our customers in developing and producing specialized products. For the pharmaceutical industry, our role is to complement and partner with drug delivery companies to provide unique materials and manufacturing expertise while relying on them for their research, regulatory, and marketing expertise.

In addition to continuing to provide adhesive components and customized drug delivery platform technologies through our Pharmaceutical and ARx divisions, we will work with our customers to plan for and anticipate the next "big thing" for the pharmaceutical industry. We are already poised to offer solutions beyond drug delivery technology for the pharmaceutical industry, such as anti-counterfeiting solutions. Brand protection and global counterfeiting is and will continue to be a major concern in the next decade. Our ARmark Authentication Technologies division develops and manufactures microscopic covert markers that can be applied directly to pharmaceutical pills and tablets or incorporated into packaging materials, such as plastic bottles, films, and labels. This technology is just another way AR can offer different solutions for pharmaceutical companies to enhance and sustain their products for many years to come. ◆

Technology Showcase

Dose by Dose Counter

The 3M™ Integrated Dose by Dose Counter provides an accurate, customizable, patient-friendly solution to guidance issued by the Food and Drug Administration (FDA) requiring dose counters for pressurized Metered Dose Inhalers (pMDIs). The robust design eliminates over- and under-counting, while the familiar look and clear display allows patients to use the device with no additional training. It's compatible with most valves and can be modified to fit your needs. By combining the 3M™ Integrated Dose by Dose Counter with our global regulatory experience, 3M can help smooth the integration process to add a dose counter to your programs. . For more information, contact 3M Drug Delivery Systems at (800) 643-8086 or visit **www.3m.com/dds.**

Transdermal Delivery

Aveva is a leader in transdermal drug delivery systems with global resources and operations that make it a quality company to partner with. Featuring a state-of-the-art facility (over 117,000 sq. ft.) located in Miramar, Florida, Aveva offers a full range of services, including a core competency in global research and development, along with fully equipped blending, coating, and packaging capabilities. Aveva has an excellent record of regulatory compliance and comprehensive quality systems. Aveva's qualified team includes Nitto Denko's global subsidiaries that can make a tremendous impact on your projects in a timely manner. For more information, contact Robert Bloder at (954) 624-1374 or visit **www.avevadds.com**.

Prefillable Delivery Systems

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

Packaging Solutions

Bilcare Research

Bilcare is a global provider of innovative packaging materials and solutions for the pharmaceutical industry. We partner with our customers and support them with a broad portfolio of film- and foil-based packaging materials to provide their drugs with the optimum protection and shelf-life as well as with specialty materials and solutions for brand protection and enhancement of brand identity. We provide research services that enable our clients to develop the optimum package by quantitatively determining the failure mode of new and existing applications using an innovative stability evaluation protocol that reduces time, cost, and resource loading. For more information, contact Remco van Weeren, PhD, at Bilcare, Inc. at (610) 935-4300 or visit **www.bilcare.com**.

Technology Showcase

Innovative Dosage Forms

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Capsugel® is the world's leading supplier of two-piece capsules. With over 140 years of production experience, Capsugel offers formulation services, patented dosage delivery technology, and liquid and precision powder-filling equipment. The new Xcelodose® system creates clinical trial batches in precisely dispensed amounts as low as 100 micrograms. With Xcelodose, capsules can be filled with drug substances alone, eliminating the need for excipient compatibility and preformulation activities. Capsugel supports clinical development with the CFS 1200™ capsule liquid-filling and sealing bench top machine for R&D Labs as well as 100- and 300-hole benchtop fillers. Products include two-piece capsules in gelatin, pullulan, and HPMC; Licaps® liquid capsules; softgels; PCcaps® for preclinical animal studies; and DBcaps® for double-blind comparator trials. For more information, visit Capsugel at **www.capsugel.com**.

Pharmaceutical Solutions

Catalent™

Catalent Pharma Solutions' services include a full range of development services, such as preclinical support, API development, analytical services, drug delivery development, clinical manufacturing, and packaging services. We have expertise in inhalation development and can offer innovative biologic cell-line development using our proprietary GPEx™ technology. Catalent's drug delivery systems include soft gelatin and Vegicaps® Soft capsules; Zydis® fast-dissolve dosage form; oral modified-release technologies, including EnCirc®, EnVel®, and EnSolv®; and a range of inhaled technologies. Along with our proprietary dose forms, we also manufacture traditional oral, sterile, topical, and inhaled dose forms. We also produce biologics for preclinical and clinical studies. Globally positioned, our packaging services include commercial packaging for all dose forms and the supply of printed components. For more information, contact Catalent Pharma Solutions at (866) 720-3148 or visit **www.catalent.com**.

Development & Manufacturing

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

Hybrid Iontophoresis Technology

Hybresis is a revolutionary drug delivery system that uses the power of iontophoresis technology. It provides clinicians with a wireless system that offers precise dose control, alternative treatment modes, and shortened in-clinic treatment times. With three treatment modes in one patch, Hybresis combines the precise dosing of traditional dose controllers with the convenience of patch-only treatments. The Hybresis mode initiates a session of Skin Conductivity Enhancement that reduces wear times, allowing patients to move on to other physical therapy activities or leave the clinic. For more information, contact Empi at (800) 328-2536 or visit **www.hybresis.com**.

Technology Showcase

Orally Disintegrating Tablets

AdvaTab® is a new generation of ODT technology that offers distinct advantages and unique applications – unparalleled taste, flexible dosing, modified release, and a robust tablet. AdvaTab can be combined with Eurand's leading Microcaps® taste-masking technology to provide an ODT with superior taste and mouth-feel. AdvaTab tablets dissolve rapidly in the mouth within 15 to 30 seconds, and the smooth mixture of carrier excipients and taste-masked drug granules is suitable for delivering high drug doses. Modified-release drug granules can also be incorporated into the AdvaTab dosage form to provide a fast-dissolve tablet with sustained-release properties. AdvaTab tablets can be packaged in either bottles or push-through blisters. For more information, contact Eurand at (937) 898-9669 or at **bizdev@eurand.com**.

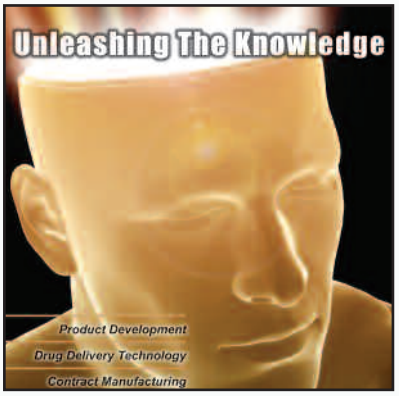
Polymers & Delivery Technologies

Pharma Polymers is one of the world leaders in the manufacturing and supplying of functional coatings for the pharmaceutical industry. EUDRAGIT® polymers are ideal for enteric delivery, controlled release, and protective coatings. Based on more than 50 years of experience in EUDRAGIT polymer design and formulation know-how for pharmaceutical applications, Pharma Polymers has developed intellectual property on advanced oral drug delivery technologies. The different brands of EUDRAPULSE®, EUDRACOL®, and EUDRAMODE® are the achievements of this intensive research and development effort so far. Pharma Polymers' business models for commercialization of these drug delivery technologies range from the development of customer-specific solutions to out-licensing strategies. For more information, contact Evonik Degussa Corporation at (877) 764-6872 (option 4) or visit **www.pharma-polymers.com.**

Drug Delivery & Development

Galenix, a pharmaceutical drug delivery and drug product development company, includes 3 business units to manage the development process from the molecule to the registration of the medicinal product according to GMP Europe and FDA standards. Galenix Pharma is dedicated to clinical trial batch manufacturing and packaging and quality control. Galenix Development is a research and development company focusing on drug delivery systems, which include Microgix, Minextab, Minextab/Floating, and Mucolys. Galenix Innovations carries out technology surverys, innovating formulation design and feasibility studies for patented technologies used by pharmaceutical laboratories. Galenix runs its own drug product development programs from the sourcing and characterization of APIs to marketing and outlicensing to pharmaceutical companies. For more information visit Galenix at **www.galenix.fr**.

Pharma Development Services



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

Technology Showcase

Manufacturer & API Specialist

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

Delivery & Specialty Pharma

Penwest has a clear, well-defined growth strategy: to leverage its strength in drug delivery and drug formulation to develop a portfolio of products targeting disorders of the nervous system. The company's current development pipeline includes products for the treatment of pain, epilepsy, Parkinson's disease, spasticity, and edema. It is continually evaluating new growth opportunities, both internally and externally. During 2006, Penwest made important progress in pursuit of that strategy. Its key accomplishments included the approval and launch of Opana ER® by Endo Pharmaceuticals, development of its internal pipeline, and enhancement of its organizational capabilities and processes. For more information, contact Penwest at (845) 878-8400 or visit **www.penwest.com**.

Pharmaceutical Product Development

Licensing opportunities for PharmaForm's patented transdermal and transmucosal delivery systems are available. PharmaForm's proprietary delivery platform is a versatile polymeric delivery system that can be applied to many drug candidates and product applications. The company's Drug Delivery Technology team is integrated with formulation development, analytical, materials, and manufacturing groups to develop and optimize transdermal systems. The Formulation and Product Development and Analytical groups work closely to plan and execute the numerous facets of system development activities. After formulation development, clinical assessment, and final formulation selection is complete, PharmaForm can scale-up your product for commercial manufacture. PharmaForm will combine its pharmaceutical expertise, formulation chemistry, and long history of know-how to develop a high-quality transdermal drug delivery system for your market application. For more information, contact PharmaForm at (512) 834-0449 or visit **www.pharmaform.com**.

Controlled Delivery Platform

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

DRUG DELIVERY Executive
CIMA LABS
a Cephalon company

CIMA: Now More Than ODTs

Raj Khankari, PhD, MBA

General Manager, CIMA & VP Worldwide Drug Delivery Technologies, Cephalon

"If a partner is looking for a superior technology-driven product, then they should talk to us. We have the infrastructure to support your drug's development with experienced scientists, quality manufacturing, and solid project management."

CIMA® has more than 15 years of experience in the development and manufacturing of pharmaceutical products, and its name has become synonymous with orally disintegrating tablet (ODT) dosage forms. After establishing itself as an ODT leader, CIMA expanded into new drug delivery platforms. The development of the CIMA enhanced oral transmucosal platform, OraVescent®, resulted in the product, Fentora® (fentanyl buccal tablet, C-II) for breakthrough cancer pain in opioid tolerant patients with cancer. CIMA continues to build its third-party partnering business. Furthermore, CIMA can now offer additional drug delivery technologies that have become a part of the CIMA technology portfolio due to its acquisition by Cephalon. Drug Delivery Technology recently interviewed Dr. Raj Khankari, General Manager of CIMA and Vice President of Worldwide Drug Delivery Technologies for Cephalon, to gather his insights on the drug delivery business and to understand how CIMA is poised to maintain and grow its drug delivery technology platforms for its partners.

Q: CIMA just passed its 3-year anniversary in August since being acquired by Cephalon. Congratulations. How are things going?

A: Thank you. CIMA is doing very well. We became a wholly owned subsidiary of Cephalon in 2004 with the idea that CIMA would become the "brand" for the Cephalon drug delivery partnering business. All of Cephalon's Drug Delivery technologies are now consolidated under the CIMA brand. We work with partners to develop and manufacture products utilizing our technology platforms just as we did under our original drug delivery business model. The upside is that now we can offer technologies and manufacturing capacity from all of the Cephalon drug delivery sites.

Q: How have your technology platforms changed since becoming a subsidiary of Cephalon?

A: CIMA now represents three drug delivery sites located in Utah, France, and our original Minnesota facilities. We currently offer several commercialized technologies for partnering and have others that are in development. These technologies include oral transmucosal delivery technologies, OraVescent and OTS®; orally disintegrating technologies, OraSolv®, DuraSolv®, and Lyoc™; granular formulations; and a solubilization technology, MicroSolv™. France's Lyoc technology was the first commercialized lyophilized orally disintegrating wafer. They have successfully launched eight products to date. We have just installed a new GMP manufacturing line for Lyoc products to

increase our capacity for potential partners.

The US sites work together on new oral transmucosal technologies. Utah's expertise with its OTS product, Actiq® and Minnesota's expertise with its OraVescent product, Fentora have been combined and are available to our partners.

In Minnesota, we also naturally focus on our ODT technologies, but recently, we have seen an increase in interest for sachet formulations, specifically for pediatric and geriatric indications. Our taste-masking expertise that we use for ODTs is used for these products. We are currently talking with several potential partners about this technology and hope to have commercial product running on our granule-filling line in Minnesota in the near future.

On the new technology front, CIMA is also developing MicroSolv™. It is a solubilization technology for poorly soluble molecules. The finished product can be oral tablets, capsules, or ODTs. Data to date is promising, and we expect that it may afford some advantages over existing solubilization technologies.
In an effort to further expand our capabilities, we are also actively seeking in-licensing and collaboration opportunities for new drug delivery technologies.

Q: What kind of experience should partners expect at CIMA?

A: If a partner is looking for a superior technology-driven product, then they should talk to us. CIMA has established itself as a drug delivery partner who is a one-stop shop. We have the infrastructure to support your drug's development with experienced scientists, quality manufacturing, and solid project management. This attention to project details continues through commercialization when the partner's product is handled by our alliance management group. Throughout the process, the partner will experience a professional, turn-key operation. CIMA does tailor partner development programs to meet their individualized needs. For example, CIMA can manage a bioequivalency clinical trial for a partner if they do not have the expertise or desire to manage it themselves. CIMA partners also rely on fast development timelines, our strong regulatory record, and established manufacturing processes.

Q: What do you believe is the future of drug delivery, and how is CIMA shaping this future?

A: I believe the future of drug delivery is innovative technologies that produce products with a strong value proposition. With the entry of generic drugs and the low number of new chemical entities being approved, drug delivery will continue to offer differentiation and extend the life cycle of many products. Drug delivery technologies offering better pharmacokinetic profiles, targeted drug delivery, and novel enhancements to protein and peptide delivery will continue to be emphasized. These developments will help our partners to provide drugs that better serve both patients and physicians.

CIMA is moving into new areas of unmet needs in drug delivery. One such enabling technology area is enhanced oral bioavailability. Many new chemical entities are lost in discovery due to their physico-chemical properties that prevent them from becoming a product. Drug delivery technologies, like MicroSolv, have the opportunity to turn a therapeutically superior yet insoluble molecule into a drug product. Overall, I think it is an exciting, dynamic time to be in drug delivery. ◆

SPECIALTY PHARMA
Strategies For Business Development

Ophthalmic Therapeutics

Advancing Delivery of Ophthalmic Therapeutics Through Iontophoresis

By: **Stephen From,**
President & CEO, EyeGate Pharma

FIGURE 1

The EyeGate® II Delivery System Applicator

Introduction

The development, or lack of development, of novel therapeutics for serious eye diseases throughout the past 20 years has focused attention on the need for a convenient, safe, and efficient delivery technology for many existing ocular drugs. These medications may require topical installations, systemic administration, intravitreal or periocular injections, or sustained release vitreous and subconjunctival implants — each with its risks and disadvantages that leave patients and physicians with limited options. A particularly painful reality for wet age-related macular degeneration (AMD) patients, despite the availability of Macugen®, Lucentis®, and the colorectal cancer drug Avastin®, used off-label by physicians to treat this disease, is the need for invasive administration via regular intraocular injections.

Topical administration, while successfully used to treat diseases such as glaucoma, inflammation, and other external eye diseases, delivers as little as 5% of a given drug to the anterior eye segment and can't provide the therapeutic drug levels needed to treat vitreoretinal eye diseases. Systemic delivery of ocular therapies requires that these drugs cross the retinal barrier to get at target eye tissues, necessitating relatively high dosages and associated drug toxicities. Medications such as prednisone, cytotoxic agents for treating intraocular inflammation, and antivirals may cause severe side effects at doses needed to achieve the desired therapeutic effect in the eye when delivered systemically. Other medications requiring local delivery to the posterior segment of the eye, such as Macugen and Lucentis, must be administered by specialists via an intravitreal injection. These are difficult procedures for patients that can and do lead to complications, including increased intraocular pressure, vitreous hemorrhage, retinal detachment, and endophthalmitis. Another example, Retisert™, the fluocinolone acetonate implant used to treat non-infectious posterior uveitis, achieves sustained release of constant drug dosages, but it may also have the same side effects as injections, and the dosage cannot be modulated. Implants must be surgically placed, and once the drug has been completely released, the implant must be surgically replaced. Continued development of new ophthalmic therapeutics that address the current $11-billion market as well as the needs of an aging population requires a safe, practical, and accessible drug delivery technology that can be readily used by ophthalmologists.[1]

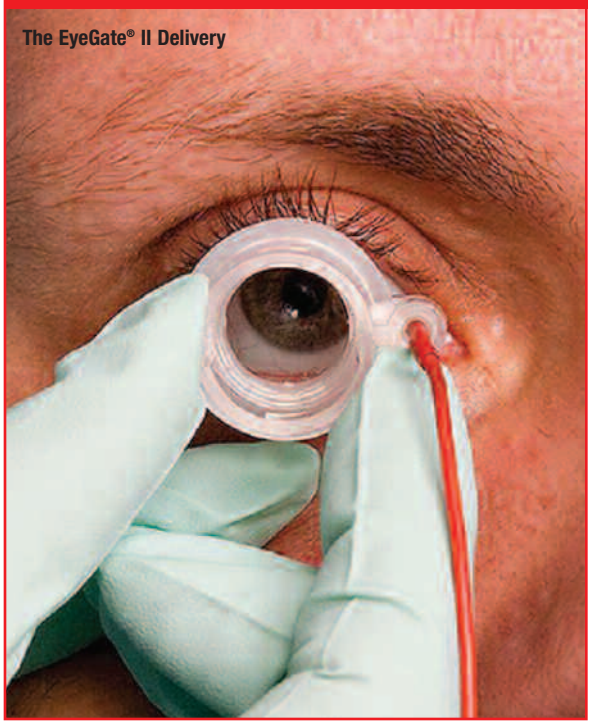
Coulomb Controlled Iontophoresis (CCI) for Non-Invasive Ophthalmic Drug Delivery

As a potential alternative to current ocular delivery technologies, EyeGate Pharma is commercializing a non-invasive iontophoretic drug delivery system, the EyeGate® II. The company was founded in France in 1998, with technology licensed from Bascom Palmer Eye Institute at the University of Miami, and developed by Dr. Jean-Marie Parel and Dr. Francine Behar-Cohen. In 2006, the company moved to Waltham, MA, to advance commercial development of The EyeGate II Delivery Platform. At that time, the company also

FIGURE 2

Transfer syringe is used to fill the applicator with the drug.

FIGURE 3



refocused its business, transitioning to a Specialty Pharmaceutical model in recognition that successful iontophoretic drug delivery requires adaptation of individual drugs. EyeGate has since expanded its senior management and research and development teams and gained ISO 13485 certification in preparation for bringing the EyeGate II Delivery System through clinical trials and the regulatory approval process in the US and Europe.

EyeGate's ocular drug delivery platform works through iontophoresis, a technology currently used to deliver certain pain medications, such as fentanyl, anti-inflammatories, and corticosteroids transdermally. Iontophoretic drug delivery occurs through enhanced transport of molecules through cells and tissues using the driving force of an applied electric field. Specifically, an electrical field created by a low-level of electrical current is used to hydrolyze water and to modify the permeability of the cells so that the ionized drug can be delivered through different tissues to targeted areas in an efficacious quantity. When either positively or negatively charged drugs are applied across a membrane with an electrode of the same charge, the like charges repel each other. This repulsion causes current to flow from the application electrode across cell membranes and back toward the oppositely charged electrode, thereby propelling a charge-bearing drug into target tissue.

In order to effectively deliver ophthalmic drugs iontophoretically, a technology should be able to deliver a range of therapeutics to both the anterior and posterior tissues of the eye, and the drugs must initially be adapted for iontophoretic delivery. EyeGate has concentrated its efforts on optimizing the EyeGate II Delivery System (Figure 1) and developing a highly specialized laboratory dedicated to formulating drugs for this delivery method. The EyeGate II Delivery System was specifically designed by ophthalmologists for transscleral delivery. It consists of a small 9-V battery-powered generator and a disposable applicator with a transfer syringe that is used to fill the applicator with the drug (Figure 2). The annular (circular) design of the drug delivery applicator provides a larger contact area that decreases tissue current density, while the increased electrode size dissipates heat. The inert electrode composition eliminates the need for exogenous ions and minimizes delivery time to less than 5 minutes.

These device design innovations provide safe and effective transcleral (white of the eye) delivery of a range of therapeutics throughout the anterior and posterior tissues of the eye. The iontophoresis delivery technology is coulomb-controlled, meaning it automatically regulates delivery of each drug unit used for treatment by keeping the current constant in the iontophoretic circuit.

EyeGate has been working with corporate research partners on formulating their particular drugs to enable their iontophoretic delivery. Some potential partners are looking for non-invasive ways to deliver their new chemical or biologic entities, while others are looking for innovative ways to extend patent life with novel reformulations via iontophoretic delivery.

Key reformulation factors include overall compound charge, compound solubility in aqueous solutions, and stability. The company now has in place a state-of-the-art formulation laboratory where it optimizes drugs for iontophoretic delivery and is currently focused on how to deliver larger biologics, including proteins and oligonucleotides like siRNAs. We have shown we are not only able to deliver siRNAs, but can also achieve increased cellular uptake facilitated by current-induced permeability changes in cell membranes.[2] We believe we can adapt

Getting to market should feel like a sprint, not a marathon.

[And our skilled team will make every transition successful – from start to finish]

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- **Finished Dosage Form**

That's why you need Team DSM. DSM Pharma Chemicals excels in seamless transitions from one stage of a product's development to the next. From our detailed cGMP workflow management systems to our self-auditing control procedures, DSM Pharma Chemicals is always aware of your product's status in the development and scaling-up process. So when you're a customer, rest assured that your product is fully documented and prepared on time, exactly as ordered, for manufacture (and a first place finish). But that's just part of the DSM package of solutions.

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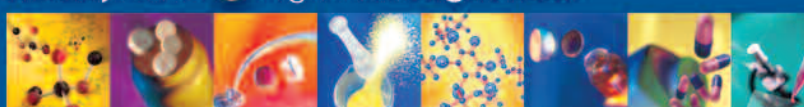

a variety of drugs, including small molecules, oligonucleotides, peptides, and proteins for delivery with EyeGate II and encourage ophthalmic drug developers to consider working with us in formulating their drug candidates for non-invasive iontophoretic delivery.

Promising Results

While ophthalmologists have been testing ocular iontophoretic drug delivery, for example, gentamicin for intraocular infection and foscarnet for cytomegalovirus (CMV) infection for more than 15 years, we believe EyeGate's platform represents the first serious attempt at practical commercialization of this technology, as well as a fundamental advance in ocular drug delivery. In our proof-of-principle study completed with our first-generation device, we demonstrated that we could safely deliver a steroid to treat various types of severe ocular inflammation.

Eighty-nine patients with inflammatory ocular diseases participated in a pilot study involving 216 applications of methylprednisolone hemisuccinate (HPM), a corticosteroid used to treat corneal graft rejections, macular edema, uveitis, and other inflammatory eye diseases. After administration of a local anesthetic, 2 ml of HPM were administered daily using our prototype device for, on average, 3 consecutive days with an application time of 2 to 4 minutes at 1.2 to 2 mA of current (Figure 3).

Results showed that visual acuity improved among all the treated patient groups (mean 20/400 to a mean of 20/125 by day 30), no patient lost vision, and 90% of patients experienced no or only mild discomfort during three consecutive applications, resulting in significant decreases in concentrations of aqueous proteins and other inflammation markers that occurred by day 10. Any minor irritations resulting from the procedure resolved within 24 hours. Based on these encouraging results, we plan to initiate a clinical study in H1 2008 testing drug delivery with EyeGate II for acute uveitis flare-up treatment.

Summary

To date, EyeGate has raised $16 million in venture funding and expects to raise another round in 2008 to fund its clinical development programs. Iontophoretic drug delivery is not new, and there is a clear need for expanding its use. It has been well studied and has been FDA approved for certain dermatologic applications. We believe that EyeGate Pharma is the only company to have successfully advanced the use of iontophoresis to safely and effectively deliver medication to both the anterior and posterior tissues of the eye, and to offer a clear alternative to invasive, less-effective, potentially unsafe, and difficult-to-use ocular delivery methods.

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Stephen From

President & CEO
EyeGate Pharma

Mr. Stephen From was formerly a Senior Executive and Chief Financial Officer at Centelion SAS, a 100-person independent biotechnology subsidiary of sanofi-aventis with a Phase II biological drug for the treatment of peripheral vascular disease. Previously, he was an Investment Banker specializing in the biotechnology and medical device sectors and was most recently at Bank of America Securities as Director in the Global Healthcare Corporate and Investment Banking Group and Head of European Life Sciences.

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Monoclonal Antibodies

Improving Therapeutic Antibodies

By: Jeff Morhet, Chief Executive Officer & Chairman, InNexus Biotechnology Inc.

Introduction

Monoclonal antibodies (MAbs) have been one of the great successes of modern medicine, and biotechnology's greatest medical achievement. Of the 500 protein drugs in clinical testing today, no fewer than 300 are MAbs. In 2005, Business Communications Company estimated the worldwide market for MAbs at $15 billion, or nearly one-fourth of the world protein therapeutics market. Sales of therapeutic MAbs are projected to grow to $26 billion by 2010, an average growth rate of 11% per year. Interestingly, MAbs enjoy a long product life cycle. According to a report by Arrowhead Publishers, sales of the oldest three MAbs on the market today (Rituxan, Remicade, and Synagis), all approved in the late 1990s, are still growing.

Antibodies are very large proteins containing a constant region and a variable region. The variable region possesses chemical affinity to specific antigens or epitopes. For medicinal MAbs, the epitope target is usually a molecule implicated in disease. In cancer therapy, the MAb binds to cancer cell surface antigens, and through any one of several complex mechanisms, induces cell death. In the case of autoimmune disease-fighting MAbs, the antibody binds to and inactivates disease-mediating inflammatory molecules.

Among the leading blockbuster MAb treatments are the oncology drugs Rituxan (rituximab/non-Hodgkins lymphoma; Genentech/IDEC), Herceptin (trastuzumab/breast cancer; Genentech), Avastin (bevacizumab/colorectal cancer; Genentech), and Erbitux (cetuximab/colorectal cancer; Bristol-Myers Squibb, Imclone). Each of these drugs works by targeting and binding to a disease-specific protein on cancerous cells. MAbs are not limited to cancer treatment. One of the earliest approved antibody treatments was OKT3 (muromonab-CD3/transplant rejection; Ortho Biotech). At least five other MAb products have been approved in the United States for a range of autoimmune diseases, including Humira (adalinumab; Abbott), Remicade (infliximab; Centocor), and Raptiva (efalizumab; Genentech).

MAbs are increasingly viewed as "targeted" or "personalized" therapies because of their specificity. For example, the blockbuster breast cancer drug Herceptin is administered only to women who are high expressers of the HER2/neu gene, which is present in most breast tumors to varying degrees. The more copies of the gene a tumor expresses, the more susceptible it is to treatment with Herceptin. Only about 25% of women with breast cancer respond to the drug. Similarly, only 48% of non-Hodgkins lymphoma patients respond to Rituxan, which targets the CD-20 antigen.

Making MAbs Better

Historically, a problem with MAb treatments has been immunogenicity directed at foreign proteins, even those that are beneficial. Early therapeutic antibodies patterned on mouse proteins gave rise to human-anti-mouse antibodies (HAMAs), which limited the number of times a patient could be dosed with the MAb. Subsequently, chimeric or partially humanized antibodies were developed that were more human-like in their appearance to the immune system. Today, at least two companies, Medarex and Abgenix, claim to possess manufacturing technology that generates fully human antibodies. There has been significant interest in modifying protein therapeutics to improve pharmacokinetics, safety, and efficacy. In the early 1990s, Altus Biologics introduced cross-linked enzyme crystals (CLECs), which were dimers of common enzymes hard-wired together by covalent chemical bonds. This chemical linking of two identical proteins was never successfully applied to therapeutic agents. However, as we will see, the idea of MAb molecules aggregating (but only at the active site) can be a powerful strategy for improving the therapeutic properties of antibodies.

Perhaps the most significant modification to therapeutic proteins to date has been PEGylation — the

attachment of very large polyethylene glycol residues, which greatly improve the circulating half-life of a protein. Among the blockbuster PEGylated protein products are Amgen's Neulasta (pegfilgrastim), a PEGylated version of granulocyte colony stimulating factor used to boost white blood cells, and Roche's Pegasys PEGylated alpha interferon for treating hepatitis. In both cases, PEGylation improves the efficacy of the protein and reduces dosing. Most importantly, PEGylation demonstrated that chemical modification could make complex protein drugs more effective.

The most significant modification to MAbs has been the introduction of fully humanized antibodies, which are much less likely to cause adverse immunologic responses than are murine antibodies. However, generation of fully humanized antibodies is a ground-up approach that involves serious molecular biology, years of product development, and a high risk of failure.

It turns out that the combination of chemical modification and aggregation can significantly improve the activity of disease-fighting antibodies.

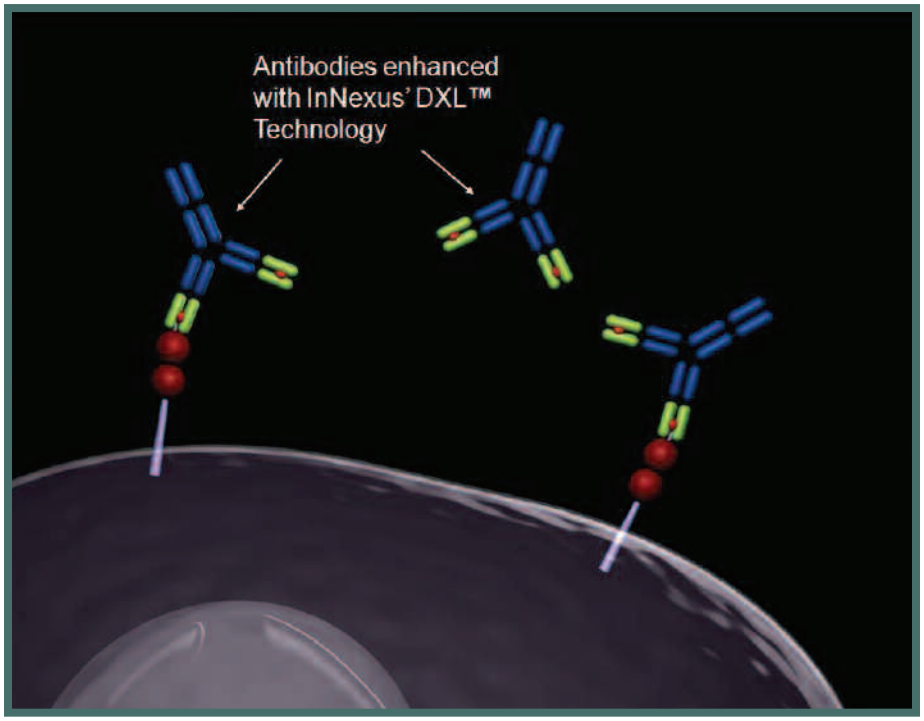

Figure 1.

Factors Affecting Potency

Safety aside for a moment, the effectiveness of a MAb treatment depends on several factors, including the natural affinity of the antibody for the target, and the avidity of that interaction. Although the terms are sometimes used interchangeably, there are subtle differences between affinity and avidity. Affinity relates more to the native binding strength between one binding site and one antigen, whereas avidity takes the valency of binding into account. An MAb with four binding sites will have greater avidity for the target than an MAb with only one binding site, which suggests that multi-valency of binding will cause antibody and target to bind more strongly. For antibody treatments, that means a higher level of efficacy per unit of antibody. Antibody-target interactions of higher avidity could achieve the desired therapeutic effect at a much lower antibody dose, which is highly desirable for reducing side effects and lowering the cost per manufactured dose.

Avidity enhancement could also change the current view and approach toward personalized or targeted therapies. Herceptin has become the poster-child for such treatments, which seek to match patients possessing specific genotypically defined diseases with drugs that target those genotypes. Along with numerous benefits, personalized medicine presents a unique ethical dilemma: What to do for patients whose genotypes suggest no treatment will work? The answer in the case of small-molecule drugs is probably to do nothing because ineffective treatments can cause more harm than good. The bright news is that identifying drugs that are effective for certain genotypes should goad companies into revisiting the vast number of compounds that have failed in clinical trials due to less-than-stellar efficacy or unacceptable toxicity. Resurrecting rejected drugs will not be an exercise for the faint-hearted, as clinical development "initially rejected drugs would need to be tested at least in Phase II and Phase III" is extremely expensive. Yet, for some diseases, it might be more cost-effective than beginning from scratch.

Luckily for MAb drugs an intriguing alternative exists that would most likely entail a far less-costly route to expanding a drug's label. One possible way to improve efficacy of an antibody treatment is to improve target binding, but that involves basic discovery of new antibody molecules, which is fraught with risk. A more attractive possibility involves increasing the number of effective binding sites on the target, which would raise an MAb's avidity and make it more effective per administered dose.

Such a strategy would achieve several goals. More effective antibodies would require lower dosing to achieve the therapeutic effect for which the drug was initially approved. Conversely, patients could benefit from significantly higher efficacy at the same or higher dose. In both situations, developers of therapeutic MAbs would provide more highly effective treatments at lower or equal production cost per dose.

Within the context of targeted or personalized medicine, improved avidity would broaden the numbers of patients considered candidates for a drug. For

example, cancer cells in approximately 75% of women with breast malignancies do not express enough HER2/neu antigen to make treatment with Herceptin worthwhile. Improving the avidity of the Herceptin-target interaction several-fold could generate many more candidates for treatment with the drug, and increase Herceptin's market share from 25% to perhaps 80% or 90% of all breast cancer patients.

The implications of avidity-enhancing strategies for future MAb-based treatments are immense. Although approval rates have historically been higher for MAbs than for small-molecule drugs, antibodies do indeed fail in clinical trials.

Fully humanized MAbs have an approval rate of 25%, more than 10 times that of early stage small-molecule drugs. That is the "glass one-quarter full" view. The other way to look at these approval rates is that historically, 75% of these drugs fail for either toxicology or efficacy. How many MAbs might be rescued by appropriate modification to higher avidity is anyone's guess. Given the cost of Phase III failures, many sponsors would attempt to salvage antibody medicines by pairing them with an appropriate genotyping test, or if a suitable technology for improving avidity existed.

Amid the euphoria over Avastin, which analysts recently predicted would soon enjoy worldwide annual sales of $7 billion, one should remember that the drug failed to achieve clinical endpoints in its breast cancer Phase III trial. Herceptin was almost not approved because of less-than-stellar efficacy during Phase III testing. Were it not for the genotyping test for the HER2/neu gene, Herceptin would have been a failed drug instead of a $1.5 billion blockbuster (sales projected for this year). Similarly, BMS/Imclone's Erbitux had more than its share of approval troubles. A more effective form of this MAb product might have hit the market up to 1 year earlier, and by now achieved a larger number of indications than it now enjoys (colorectal, head, and neck cancers).

Other MAb products were not so lucky. Roche's R1549, a radiologic-antibody combination drug, failed to show any efficacy in Phase III testing in ovarian cancer. And the multiple sclerosis drug Tysabri (natalizumab; Biogen-Idec), was voluntarily withdrawn and then re-approved, but with severe "black box" restrictions due to safety issues.

Antibodies also fail during clinical trials because of unwanted side-effects. For example, the anti-tumor necrosis factor antibodies Enbrel and Humira may cause immune suppression, while the anti-CD3 MAbs, such as the anti-rejection drug OKT3 (which has also been tested in new-onset type 1 diabetes), attacks all T-cells, not only those involved in disease.

Enhancing Avidity

Dynamic Cross Linking (DXL), under development at InNexus Biotechnology, improves an antibody's avidity for its target without affecting critical binding or immunogenicity factors. DXL is based on the discovery that certain naturally-occurring antibodies bind to one another, as dimers, after they attach to a target. Researchers noticed that these antibodies contained a peptide sequence of about 24 amino acids consisting of two regions, at opposite ends of the sequence and separated by several amino acids. When these antibodies bind to their target the first sequence on antibody "A" binds to the second sequence on antibody "B" through typical electrostatic and hydrophobic interactions. The sub-sequences may also loop around and bind to one another.

Investigators named this interaction "inverse hydropathy" and found that they could create antibody dimers by inserting the identical sequences into non-binding regions of other antibodies. In most cases the added amino acids did not alter the antibody's affinity for the target, even when more than two antibodies bridge relatively distant antigens.

In effect, an antibody bound to a target cell now provides, through this "magic sequence," a second point of attachment to the target in addition to the antigen. Multiple, crosslinked antibodies thus provide long-lived binding that gives whatever cell death mechanism prevails for a lone antibody a wider operational window. The effect has been observed for many antibody-antigen pairs and several key cell-killing mechanisms, including complement-dependent cytotoxicity, antibody-mediated cytolysis, cellular internalization of the antibody-antigen complex, and apoptosis.

Compared with unmodified MAbs, DXL-modified antibodies maintain a larger therapeutic mass on the target antigen for a longer time period, effectively increasing the half-life of the drug and providing the various mechanisms of cell death with a longer time period in which to act.

DXL amplifies the normal effect of antibodies by clumping the antibodies at the target as circulating therapeutic antibodies are only bound to their target in the presence of the target at any one time. Because they enjoy another point of attachment, DXL-modified antibodies concentrate the therapeutic antibody dose on the target, where it belongs, resulting in a several-fold improvement in binding.

For example, in one apoptosis experiment 50% of cells were killed in three days using an anti-CD20 MAb modified with the affinity sequence, whereas only 12% of cells treated with unmodified anti-CD20 died. The effect of DXL is therefore to improve the avidity of an antibody treatment rather than improving the innate binding to the antigen. Interestingly, DXL-modified antibodies do not dimerize in solution, but only when they are close enough together or one is immobilized.

InNexus recently announced its first DXL-modified antibody to enter preclinical development, DXL625 (CD20). InNexus is evaluating several additional therapeutic MAbs in their preclinical program including anti-CD19 and anti-CD20 targeted antibodies. These have been antigens implicated in cancers of lymphoid tissue, autoimmunity and neurodegenerative diseases. Both induced significantly higher tumor killing in mouse xenograft models than comparison antibodies). Additionally, InNexus has research programs of

HER2/neu, Ep-CAM, TNF, Caspases, HLADR, EGFR and RSV.

Figure 1 illustrates the improved binding to the CD20 antigen for DXL625 compared with the native anti-CD20 MAb. The initial response for DXL625 (CD20) is approximately two fold higher than the unmodified antibody. Even more impressive is the duration of binding, or off-rate exhibited by DXL625, which was approximately 10-fold higher than other anti-CD20 MAbs. This increase in binding avidity translates to a concrete functional improvement. Furthermore, DXL625 (CD20) inhibits DHL-4 tumor cell growth by approximately 40% compared with unmodified anti-CD20.

These physical-chemical measurements translate directly to improved cell-killing in vitro through apoptosis, complement-dependent cytotoxicity (CDC), and antibody-dependent cell-mediated cytotoxicity (ADCC). Using standard apoptosis assays on Raii and Ramos cell lines, DXL625 killed at least twice as many cancer cells as native anti-CD20. Results with CDC assays on Raii cells were even more encouraging. At antibody concentrations ranging from 1 to 20 mcg/ml, DXL625 out-performed anti-CD20 by up to 7-fold. With Jok-1 cells DXL625 killed between two and three times as many cells as anti-CD20. Improved killing in the 40% to 250% range was also observed in ADCC assays for Raii and Ramos cells.

Hurdles & Future Development

Manufacturing DXL-modified MAbs is straightforward and can be accomplished either through chemical attachment or through recombinant techniques in which the MAb is expressed with the sequence in place. The latter method will probably be preferred for clinical-grade material because it is straightforward, predictable, and GMP-worthy. The fact that DXL MAbs are entirely new molecules is both a blessing and a curse. The good news is that, being entirely new molecules, these products carry no intellectual property restrictions. Because INexus owns all the relevant patents, the entire portfolio of current MAb blockbusters is open to DXL modification. The bad news is that because these are new compositions of matter, regulatory authorities and good clinical practice suggests each one must be tested as such through a complete set of Phase I through Phase III clinical trials.

Toxicity and side effects are another unknown for DXL-antibodies. The toxicity of MAbs is a function of immune responses to the mouse-derived component of the protein, and cross-reactivity with antigens on normal cells. DXL should reduce antigenicity-related side effects because dosing per unit of effect will almost always be lower with crosslinked MAbs. Unfortunately, the higher avidity of DXL-MAbs for antigens on non-diseased cells might cause a problem unless the improved therapeutic effect outweighed the higher toxicity. Each DXL-modified antibody obviously needs to be assessed independently to determine the relative intensification in efficacy and toxicology.

In addition to rescuing molecules that fail during clinical trials, DXL technology will help create therapeutic-grade antibodies from those that are not considered worthy of clinical development. These might include reagent- or diagnostic-grade molecules, which for one reason or another, were never subjected to preclinical or clinical testing. Because the DXL modification creates a new molecular entity, companies embarking on a discovery program based on crosslinked MAbs would be afforded patent protection for the full 20 years. This business strategy is similar to the “chiral switches” of the 1990s, where even third-party developers were able to patent chiral forms of drugs previously patented as racemates.

The potential of DXL technology for improving diagnostics and reagents is similarly high. By improving the avidity of diagnostic MAbs, DXL in effect amplifies the signal and thereby improves the accuracy of a test. We expect an immediate result of DXL magnification will be a significant drop in false positives and more accurate detection of low-level antigens.

Jeff Morhet

President, Chief Executive Officer & Chairman
InNexus Biotechnology, Inc.

Jeff Morhet is Chairman and Chief Executive Officer of British Columbia-based InNexus Biotechnology Inc. Mr. Morhet's experience in the pharmaceutical industry includes positions at Baxter Healthcare, Merck and AstraZeneca. He has experience with pharmaceutical product development, manufacturing, regulatory affairs, product commercialization and working with the FDA for both drug and device applications. Mr Morhet's focus has been on cellular and intra-cellular anti-cancer drug development. Directly prior to InNexus, Morhet founded and directed Zila Biotechnology, Inc., a cancer focused comprehensive research, development and licensing business spawned from a Nasdaq-traded company where he had previously been VP and General Manager and refocused the company's long running cancer research, clinical development and manufacturing programs. He also has experience in the areas of corporate finance and investor relations. He graduated from Stephen F. Austin State University and attended the Executive MBA program at Arizona State University. He can be reached at jmorhet@ixsbio.com

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EXTERNAL DELIVERY

Why Don't More Business Executives Run For President?

By: John A. Bermingham

Ross Perot, a business leader and multibillionaire, had a lot of good ideas when he ran for President of the United States in 1992. In that election, he won 18.9% of the popular vote but no Electoral College votes. Still, that made him the most successful independent candidate ever. So why don't more business executives like Ross Perot run for a high-level office?

I believe the reason is the fundamental difference between how a business leader leads and how a political leader leads. The business leader is hired not elected. The business leader's most important responsibility is to maximize shareholder value. He or she typically reports to a Board of Directors, has his or her performance reviewed at least quarterly by the Board or a Board Committee, and has monthly, quarterly, and annual financial report cards. The business leader can be released from the company at any time and for any reason, except for an illegal reason.

The political leader is elected, not hired. The political leader, in this case the President of the United States, works hard to please the voters and will generally do or say anything that will generate enough votes to win an election. While the President has a Cabinet and Congress to contend with, the President is basically locked into the job for 4 to 8 years. The report cards are generated by polling companies.

Ross Perot acted like a business leader during his run for the Presidency and gave his open and honest opinion on issues. While many people did not agree with all of his positions, me included, you certainly knew where he stood on every issue. He was also a little weird but so what? So I've been thinking about how a political leader would lead a company.

In this case, the political leader, (let's refer to him/her as the CEO) who is probably a lawyer like most political leaders, is in a staff meeting and, after listening to each of the executive staff on a proposed acquisition of another company, approves the start of the due diligence for the acquisition. The Board also approves the due diligence, and the company then begins the due diligence. During due diligence, one of the Board members has second thoughts about the acquisition and brings this to the CEO's attention. The CEO, after listening to the dissenting Board member, chooses not to take a position on the acquisition. The CEO instead takes the full Board's temperature by speaking with each member individually. The CEO then surveys the executive staff, eliciting their feedback. Everyone on the executive staff takes a neutral position so as not to cause conflict with the other staff members or the Board.

The CEO, concerned about the Board and executive staff members, directs Human Resources to poll the employees on the acquisition. All employees, knowing how political the Board and upper management are, take the same position as the executive staff member that they eventually report up to. As the due diligence proceeds, Board members, executive staff members, and employees begin to take positions on the acquisition, basically for, against, or neutral. The majority of people take the neutral position not wanting to be on the opposite side of the eventual winning faction. Not wanting to take a stand at this point, the CEO decides to hold a 3-day off-site meeting at a Caribbean Resort consisting of the executive staff, a cross-section of the employees, and a McKinsey consultant to facilitate the meeting. Total attendees – 48 people – cost $205,000. The due diligence is put on hold until after the results of the meeting are tabulated. The meeting proceeds over 3 days, consisting of full attendee meetings, small group break-out meetings, followed with each break-out group making a presentation to the attendees, charts "boarded" on the meeting room walls, and a gala dinner on the last evening to build team spirit.

The CEO makes the closing comments consisting of accolades to the attendees about teamwork, full buy-in on the decisions from the meeting, the importance of "group think," and a promise to publish the results of the meeting within 2 weeks. Because the meeting attendees never came to any specific decision, the due diligence never re-starts. The acquisition dies a quiet death. Nothing is published. But wait……there's more.

The Board members are upset they were not included in the Caribbean resort meeting, take a negative position on the acquisition because they were not included, and tell the CEO to shut the due diligence down. To which the CEO responds, "already done as I knew the Board would not be for the acquisition after all." So a competitive company acquired the acquisition target and increased shareholder value by 50%. Does this sound like your company? Our government? Your CEO? ◆

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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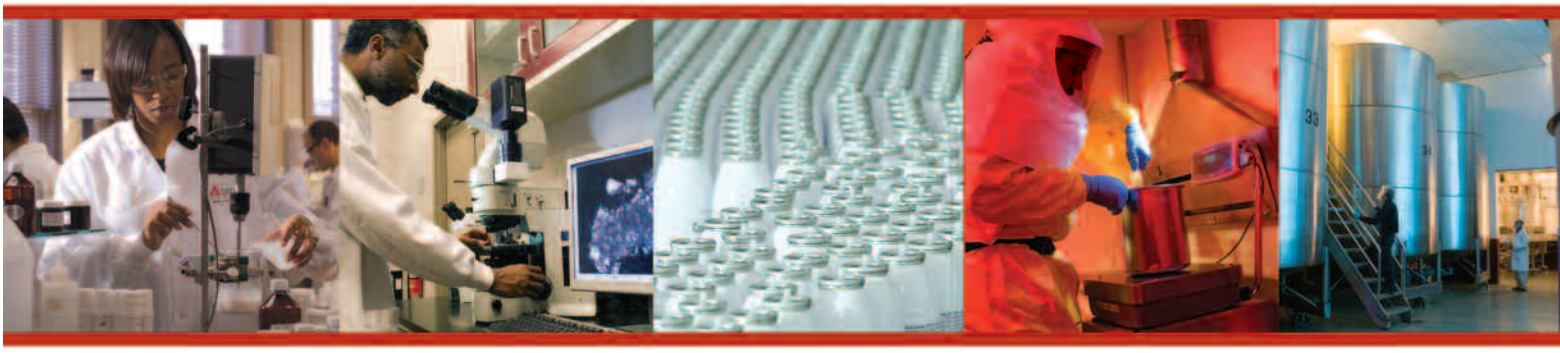

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