Drug Delivery Technology®

February 2006 Vol 6 No 2

PSAs versus Tacky Gels

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

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LESLIE J. WILLIAMS

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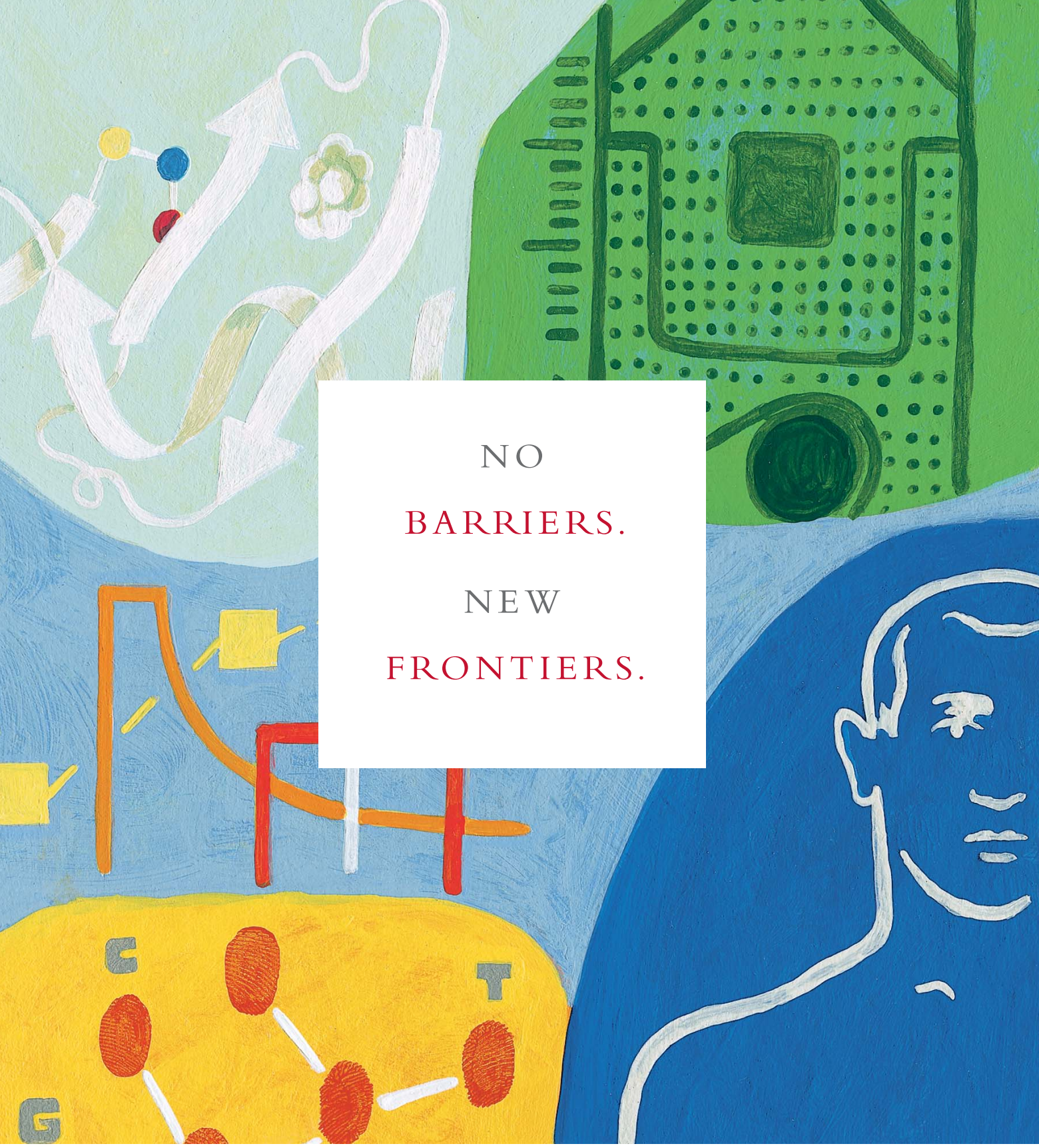

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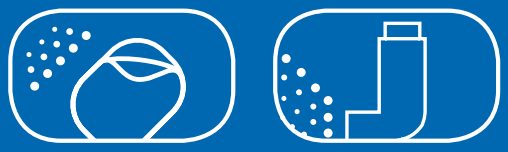

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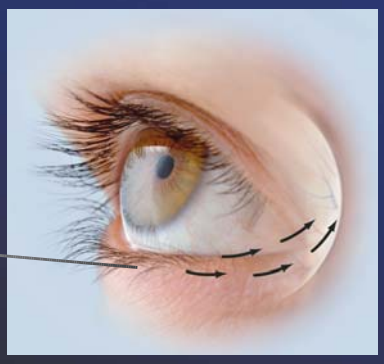

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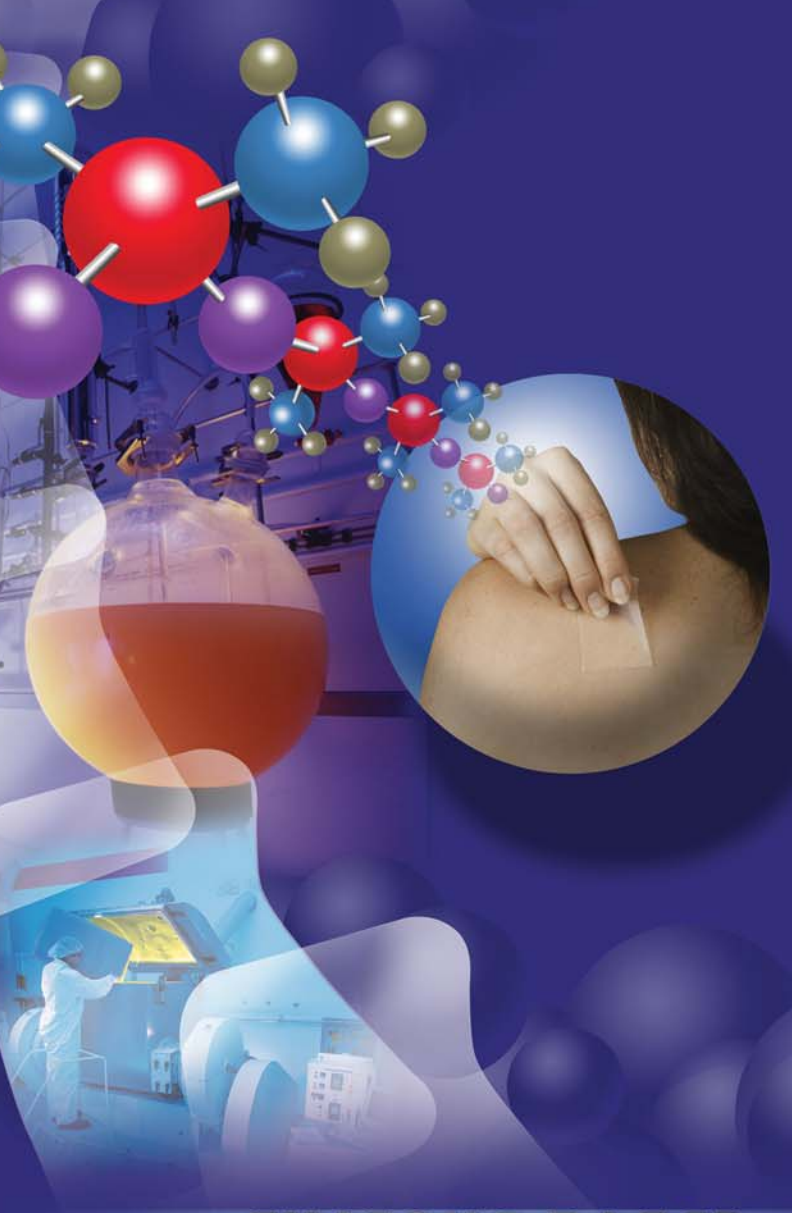

SILICONE-BASED ADHESIVES

"The discussion and data presented provide transdermal drug delivery system designers with another choice in pressure-sensitive-type, silicone-based adhesives. Silicones' historic healthcare use and drug solubility make both silicone PSAs and tacky gels good candidates for certain drug delivery applications."

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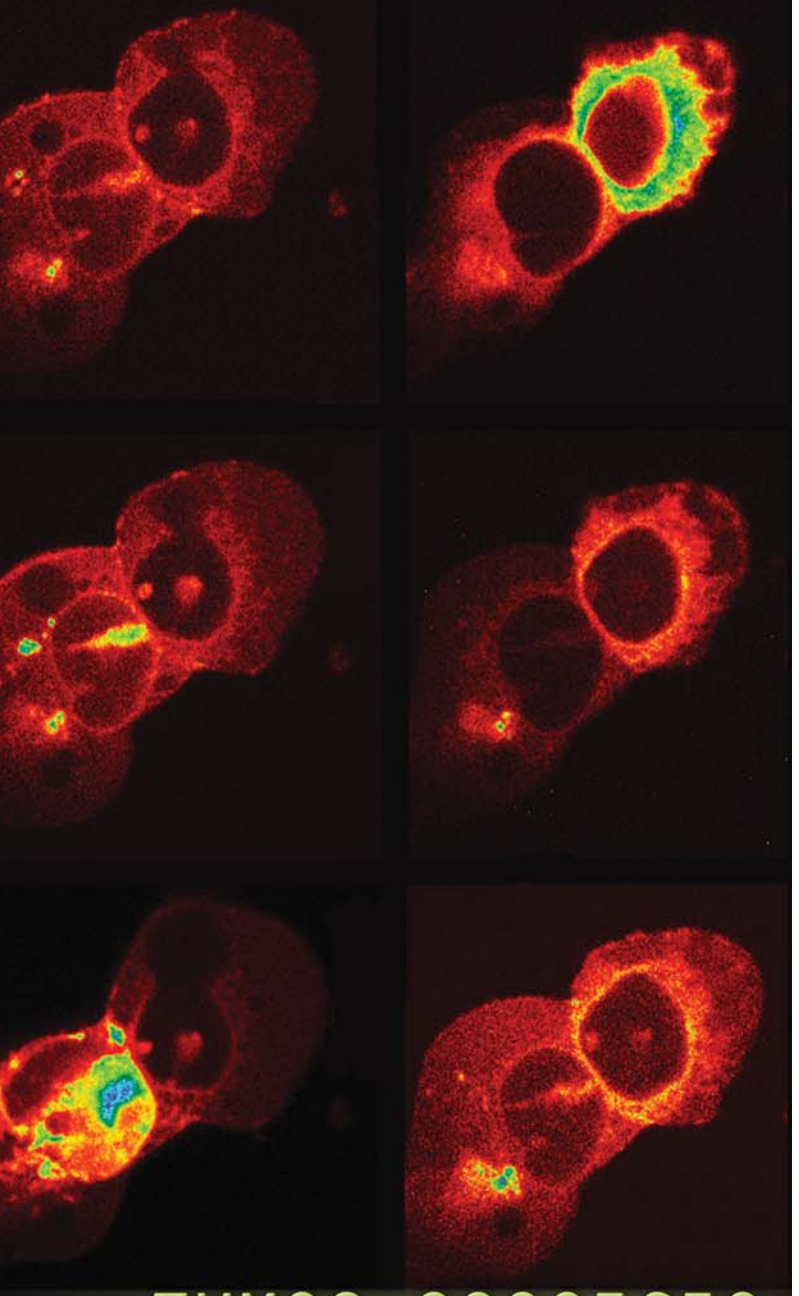

TUMOR-SPECIFIC TECHNOLOGY

"To gain maximum effectiveness and safety, tumors must be treated with an agent that only affects diseased tissue. Intralesional delivery of tumor-specific agent can further potentate the efficacy and provide an additional margin of safety."

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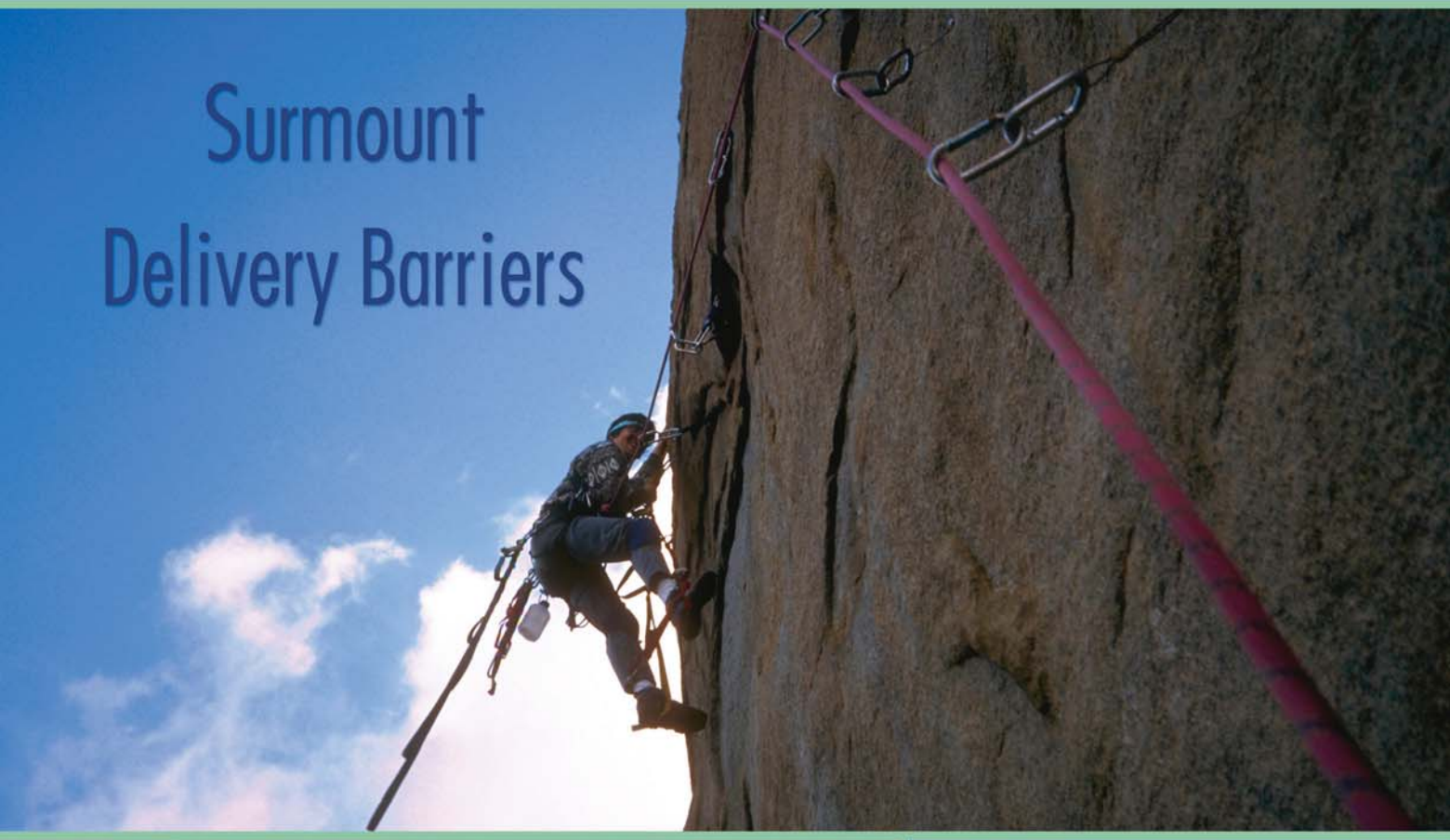

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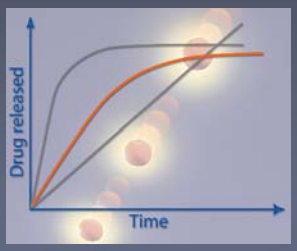

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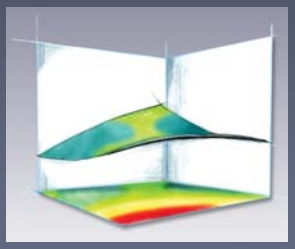
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Pfizer's Exubera Receives Approval From US FDA; Nektar Co-Developed the Inhalers & Formulation

Nektar Therapeutics recently reported that Pfizer, Inc.'s Exubera [insulin human (rDNA origin)] Inhalation Powder has been approved by the US FDA for the treatment of adults with type 1 and type 2 diabetes. Exubera was found in clinical trials to be as effective as short-acting insulin injections and to significantly improve blood sugar control when added to diabetes pills. Exubera, which is expected to be available for patients by mid-year, is the first inhaled form of insulin and the first insulin option that does not need to be administered by injection in the US.

Nektar developed the inhalers and the powdered insulin formulation for Exubera in partnership with Pfizer. Pfizer is responsible for marketing, manufacturing, and the clinical development of Exubera. Nektar provides support in the manufacturing process for Exubera insulin and manufactures the inhalation devices. Under the agreement between Nektar and Pfizer, Nektar will receive royalties on all marketed products as well as revenue for the manufacture of the powders and the inhalation devices.

"Today's FDA approval of Exubera marks the beginning of a new era for diabetes patients in the US who for the first time have an alternative to injectable insulin therapy to control their blood sugars," said Dr. John Patton, Co-founder and Chief Scientific Officer at Nektar. "Exubera would not have been possible without Nektar's innovative scientists and engineers and also our partner, Pfizer, who worked with us and remained committed to our original dream of delivering this medical breakthrough to patients."

As quoted in Pfizer's announcement, "Exubera is a major, first-of-its-kind, medical breakthrough that marks another critical step forward in the treatment of diabetes, a disease that has taken an enormous human and economic toll worldwide," said Hank McKinnell, Chairman and Chief Executive of Pfizer. "The global incidence of diabetes is currently at epidemic levels. Millions of patients are not achieving or maintaining acceptable blood sugar levels, despite the availability of current therapies. Exubera meets a critical medical need by offering a highly effective and needle-free alternative to diabetes pills and insulin injections to manage this complicated, debilitating disease."

Exubera is a rapid-acting, powder human insulin that is inhaled through the mouth into the lungs prior to eating, using the handheld Exubera Inhaler. The Exubera Inhaler weighs 4 ounces and, when closed, is about the size of an eyeglass case. The unique Exubera Inhaler produces in its chamber a cloud of insulin powder, which is designed to pass rapidly into the bloodstream to regulate the body's blood sugar levels.

Quoting Pfizer's announcement again, "Many people who could benefit from insulin are fearful of injections, so they delay treatment 5 years or 10 years, placing them at risk for serious complications. Now, for the first time, patients can improve blood sugar control with fewer or no painful injections," said Dr. William Cefalu, Exubera investigator and chief of the division of nutrition and chronic diseases at the Pennington Biomedical Research Center, a campus of the Louisiana State University System, in Baton Rouge.

The efficacy and safety profile of Exubera was studied in more than 2,500 adults with type 1 or type 2 diabetes for an average duration of 20 months. In clinical trials, many patients using Exubera reported greater treatment satisfaction than patients taking insulin by injection. Significantly more patients who had used both Exubera and insulin injections or diabetes pills reported an overall preference for Exubera.

In patients with type 2 diabetes, Exubera can be used alone as an alternative to rapid-acting insulin injections or diabetes pills, or in combination with diabetes pills or longer-acting insulin. In patients with type 1 diabetes, Exubera will be used in combination with longer-acting insulin.

Complications commonly associated with uncontrolled or poorly controlled blood sugar levels include heart disease, amputation, blindness, and kidney failure. Diabetes and its complications are estimated to account for $132 billion in direct and indirect US healthcare costs annually. Nearly 21 million Americans have diabetes and approximately 95% of these people have type 2 diabetes.

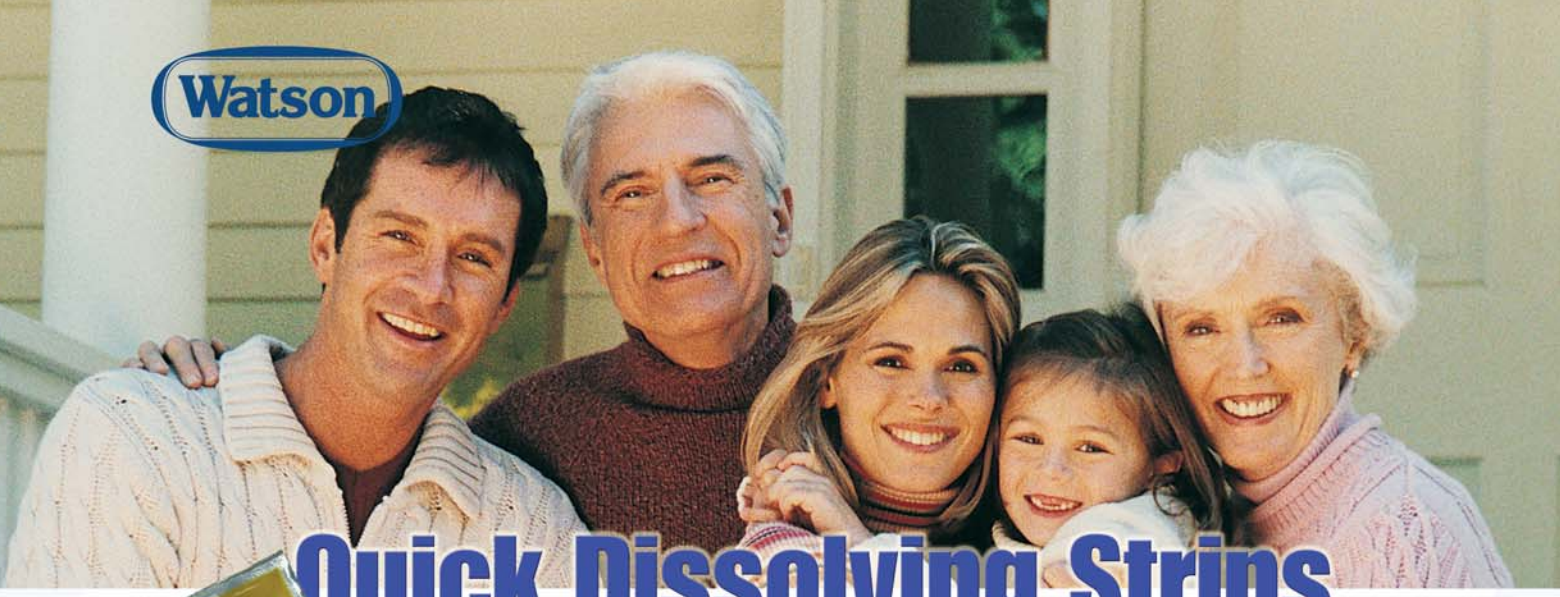
Exubera is the result of one of the most rigorous and innovative diabetes development programs. Pfizer has invested in two state-of-the-art manufacturing facilities: one of the world's largest insulin plants in Frankfurt, Germany, and a highly automated, high-tech production facility in Terre Haute, Indiana.

Exubera is a product of a collaboration between Pfizer and Nektar Therapeutics. Pfizer recently reached an agreement to acquire the Sanofi-Aventis' worldwide rights to Exubera. The two companies were previously in a worldwide alliance to co-develop, co-promote, and co-manufacture Exubera.

Patients should not take Exubera if they smoke or have stopped smoking less than 6 months prior to starting Exubera treatment. If a patient starts smoking or resumes smoking, he or she must stop using Exubera and see a healthcare provider about a different treatment. Exubera may affect lung function, so patients need to have their lungs tested before starting Exubera, and periodically thereafter, as directed by a healthcare provider. The test involves exhaling into a measuring device. Exubera is not recommended for people that have chronic lung disease (such as asthma, chronic obstructive pulmonary disease, or emphysema). Also, Exubera should not be used at all by people with unstable or poorly controlled lung disease.

Like all medicines, Exubera can cause side effects. As with all forms of insulin, a possible side effect of Exubera is low blood sugar levels. Some patients have reported a mild cough while taking Exubera, which occurred within seconds to minutes after Exubera inhalation. Coughing occurred less frequently as patients continued to use Exubera.

Nektar Therapeutics enables high-value, differentiated therapeutics with its industry-leading drug delivery technologies, expertise, and manufacturing capabilities. The world's top biotechnology and pharmaceutical companies are developing new and better therapeutics using Nektar's advanced technologies and know-how. Nektar also develops its own products by applying its drug delivery technologies and its expertise to existing medicines to enhance performance, such as improving efficacy, safety, and compliance.



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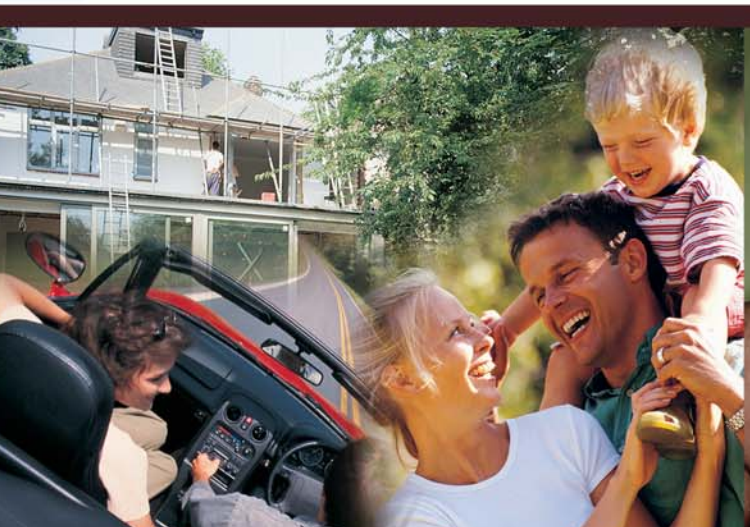

MARKET NEWS and TRENDS

Supernus Pharmaceuticals Acquires Drug Formulation Business of Shire Laboratories, Inc.

Supernus Pharmaceuticals, Inc., a newly formed specialty pharmaceuticals company, recently announced the acquisition of substantially all the assets comprising the product formulation and development business of Shire Laboratories Inc., a subsidiary of Shire plc. Founded by former SLI President and CEO Jack A. Khattar, Supernus has been funded by New Enterprise Associates (NEA) and OrbiMed Advisors.

"We are looking forward to building a premier specialty pharmaceuticals company," said Jack A. Khattar, President & CEO of Supernus. "I am grateful for the support and commitment of a strong management team and great employees at SLI. They made this acquisition possible and have been key to the successes achieved at SLI. We are also pleased to be partnering with two of the most prominent venture capital firms in life sciences."

Supernus Pharmaceuticals, Inc., is a specialty pharmaceuticals company focused on developing products for its own portfolio and in partnership with other pharmaceutical companies, using its proven and patented technologies and product development capabilities. Among its key technologies are ProScreen" and OptiScreen" for lead selection and formulation optimization, Microtrol", SolutrolTM and EnSoTrol", its oral controlled-release technologies, and AvertSM its reduced abuse potential technology.

"Our decision to acquire SLI's product formulation and development business was based on SLI's success and proven track record in developing advanced products, such as Adderall XR", Carbatrol", Equetro", and OraceaTM utilizing its unique technology platforms and capabilities," added Mr. Khattar. "We will be applying those same technology platforms and capabilities to build our own pipeline of specialty products and to continue to support our partners."

"This investment opportunity in what is a proven drug delivery company and management team is very exciting," said Jim Barrett, General Partner of NEA and Chairman of Supernus. "We look forward to working with Mr. Khattar and his team to build a leading new pharmaceutical company."

"We are delighted to partner with the management team and NEA and be part of developing Supernus into a successful specialty pharmaceuticals company," commented Mike Sheffery, General Partner of OrbiMed Advisors LLC and Board Member of Supernus.

Headquartered in Rockville, Maryland, Supernus Pharmaceuticals, Inc. is a specialty pharmaceuticals company that has a portfolio of proven and patented drug delivery technologies with full product development capabilities, including production of GMP clinical supplies in its own facility. Supernus will focus on developing differentiated products for targeted specialty therapeutic areas on its own and in partnership with other pharmaceutical companies.

pSivida Announces Several New Pharma Drug Delivery Evaluation Agreements for US Subsidiary

Global bionanotech company ***pSivida Limited*** recently announced that its wholly owned subsidiary pSivida Inc. (formerly Control Delivery Systems, Inc.) has recently entered into a number of new evaluation agreements with various companies, including large global pharmaceutical companies, to evaluate pSivida's proprietary platform technology for their developmental compounds.

The terms of the new evaluation agreements vary, but are typically 12 months in duration with the costs being born by the counterparty. With these new agreements, pSivida Limited now has evaluation agreements with 3 of the 5 largest pharmaceutical companies in the world.

In December 2005, pSivida completed the acquisition of Control Delivery Systems, a private US drug delivery company located in the Boston, Massachusetts area. Control Delivery Systems, in collaboration with Alimera Sciences, initiated a Phase III clinical trial in October 2005 to study diabetic macular edema (DME) patients treated using its Medidur platform technology to deliver fluocinolone acetonide. DME is the leading cause of vision loss for Americans under the age of 65 with approximately 500,000 treatable cases in the US alone. Medidur for DME is an injectable, non-erodible intravitreal device that is administered in an office procedure as opposed to a surgical procedure. This implant is designed to release a constant amount of drug to the back of the eye for a duration of between 18 months and 3 years.

Medidur is the next generation product to Retisert, which is administered in a surgical procedure and licensed to Bausch & Lomb for the treatment of chronic, non-infectious uveitis, a sight threatening inflammatory eye disease affecting approximately 175,000 people in the US. Retisert is the only FDA-approved back-of-the-eye treatment for uveitis. Bausch & Lomb told investors and analysts in December 2005 that they believe the future for Retisert is bright.

"We believe these new evaluation agreements come at a time when the ophthalmology market is growing strongly and are a reflection of growing interest in pSivida's technologies," said Mr. Gavin Rezos, MD and CEO of pSivida Limited. "We expect to enter into further agreements for pSivida's drug delivery products in 2006."

pSivida is a global bionanotech company committed to the biomedical sector and the development of drug delivery products in particular in oncology and ophthalmology.

pSivida owns or has the exclusive rights to use the intellectual property pertaining to BrachySil, Medidur, Retisert, and Vitrasert. The company's IP portfolio consists of 70 patent families, 74 granted patents, and over 290 patent applications. pSivida owns the rights to develop and commercialize a modified form of silicon (porosified or nano-structured silicon) known as BioSilicon, which has applications in drug delivery, wound healing, orthopaedics, and tissue engineering. pSivida has granted an exclusive license to its subsidiary, AION Diagnostics Limited, to develop and commercialize diagnostic products using BioSilicon, and has also granted an exclusive license to its subsidiary, pSiNutria Limited, to develop and commercialize food technology applications using BioSilicon.

MARKET NEWS and TRENDS

Boston Scientific & Guidant Announce Signing of Merger Agreement Valued at $27 Billion

Boston Scientific Corporation and ***Guidant Corporation*** recently announced that the Board of Directors of Guidant has unanimously approved and entered into the merger agreement provided to Guidant by Boston Scientific on January 17, 2006. Under that agreement, Boston Scientific will acquire all the outstanding shares of Guidant for a combination of cash and stock worth $80 per Guidant share, or approximately $27 billion in aggregate. Prior to entering into this agreement with Boston Scientific, Guidant terminated its merger agreement with Johnson & Johnson.

The strategic rationale, business, and growth profile of a combined Boston Scientific/Guidant should be compelling to shareholders of both companies. As a highly diversified company with leading positions in growth markets, Boston Scientific/Guidant will be one of the world's pre-eminent medical device companies, with total revenue in 2006 of nearly $9 billion.

"Guidant and Boston Scientific share an entrepreneurial spirit, highly talented employees, strong customer relationships, and an ability to pioneer life-saving therapies for patients around the world," said Pete Nicholas, Chairman of Boston Scientific. "Shareholders will benefit from the significant upside potential of the combined company, while doctors and their patients will continue to receive the most technologically advanced and highest quality medical devices and therapies. The resources and capabilities of the combined company will allow us to make further investments in our current businesses as well as pursue new revenue opportunities."

"We believe the transaction and the strategic rationale for this combination are in the best interests of our patients, employees, customers, and shareholders - reflecting the full value of our firm," said Jim Cornelius, Chairman and Chief Executive Officer of Guidant.

"The combination of these two companies provides faster, more consistent revenue growth opportunities to shareholders. We want to express our appreciation to our employees who have been dedicated to building this great company, and we all look forward to the future."

"We are excited about combining the talent and experience of Boston Scientific and Guidant employees," said Jim Tobin, President and Chief Executive Officer of Boston Scientific. "We look forward to working with Guidant to complete the transaction quickly and to creating a global leader in cardiovascular devices."

The transaction is subject to customary closing conditions, including clearances under the Hart-Scott-Rodino Antitrust Improvements Act and the European Union merger control regulation, as well as approval of Boston Scientific and Guidant shareholders. The transaction is not subject to any financing condition. Boston Scientific expects to complete the transaction by the end of the first quarter of 2006. As previously announced, Boston Scientific has entered into an agreement with Abbott under which Boston Scientific has agreed to divest Guidant's vascular intervention and endovascular businesses, while agreeing to share rights to Guidant's drug-eluting stent program. Under its agreement with Abbott, Boston Scientific will receive $6.4 billion in cash from Abbott on or around the closing date of the Guidant transaction. This amount consists of $4.1 billion in purchase price for the Guidant assets, a loan of $900 million, and Abbott's agreement to acquire $1.4 billion of Boston Scientific common stock. Boston Scientific and Guidant believe that Boston Scientific's agreement with Abbott will enable Boston Scientific and Guidant to rapidly secure antitrust approvals for the proposed transaction.

MARKET NEWS and TRENDS

Alkermes & Lilly Announce Agreement to Develop & Commercialize Inhaled Parathyroid Hormone for Osteoporosis

Alkermes, Inc., and ***Eli Lilly and Company*** recently announced they have signed an agreement to develop and commercialize inhaled formulations of parathyroid hormone (PTH). The development program will utilize the Alkermes AIR pulmonary drug delivery system. Lilly's recombinant PTH, Forteo [teriparatide (rDNA origin) injection], was approved in 2002 by the FDA for the treatment of osteoporosis in postmenopausal women who are at high risk for bone fracture and to increase bone mass in men with primary or hypogonadal osteoporosis who are at high risk for fracture. The agreement was signed after completing extensive feasibility work.

Under the terms of the agreement, Alkermes will receive funding for product and process development activities and upfront and milestone payments. Lilly will have exclusive worldwide rights to products resulting from the collaboration and will pay Alkermes royalties based on product sales.

Alkermes and Lilly will form a joint development team and will share responsibility for executing the overall development strategy for inhaled PTH. Alkermes will have responsibility for nonclinical development activities, primarily formulation testing and device development. Lilly will have responsibility for all other nonclinical development activities as well as all clinical development and regulatory activities.

"Expanding our partnership with Lilly to include the development and commercialization of parathyroid hormone provides an opportunity to leverage the experience we have gained from our inhaled insulin and human growth hormone collaborations," stated Richard Pops, CEO of Alkermes. "In addition, we believe this partnership underscores the value of the Alkermes AIR technology system, which is designed to provide patients with a simple method of delivery across a variety of diseases that may enhance treatment outcomes."

"We look forward to expanding our collaboration with Alkermes to benefit patients with osteoporosis," said Patricia A. Martin, Executive Director of Osteoporosis Products for Lilly. "We believe that the Alkermes technology has the potential to increase compliance and ultimately improve clinical outcomes for patients with osteoporosis."

The partnership to develop and commercialize PTH marks the third collaboration between Alkermes and Lilly to develop medicines based on Alkermes' AIR pulmonary drug delivery technology, which utilizes a small, easy-to-use inhaler designed to reliably deliver a broad range of doses. In 2000, the companies established an alliance for the development of an inhaled formulation of human growth hormone (hGH), currently in Phase I clinical development. In 2001, the companies entered an agreement to develop an inhaled insulin system that delivers human insulin inhalation powder (known as HIIP). Lilly and Alkermes began Phase III clinical studies with HIIP in July 2005.

Alkermes, Inc., is a pharmaceutical company that develops products based on sophisticated drug delivery technologies to enhance therapeutic outcomes in major diseases. The company's lead commercial product is the first and only long-acting atypical antipsychotic medication approved for use in schizophrenia. The company's lead proprietary product candidate, VIVITROL (naltrexone for extended-release injectable suspension), is being developed as a once-monthly injection for the treatment of alcohol dependence. The company has a pipeline of extended-release injectable products and pulmonary drug products based on its proprietary technology and expertise. Alkermes' product development strategy is twofold: the company partners its proprietary technology systems and drug delivery expertise with several of the world's finest pharmaceutical companies and it also develops novel, proprietary drug candidates for its own account.

Mylan Laboratories Signs Two Strategic Agreements With Cephalon to Utilize MTI's Advanced Transdermal Technology

Mylan Laboratories, Inc., recently announced two strategic agreements between its subsidiary Mylan Technologies, Inc. (MTI) and Cephalon, Inc., to utilize MTI's innovative transdermal technology to address certain pain and central nervous system disorders. Under the terms of the agreements, Mylan and Cephalon will collaborate with the intent to create branded transdermal products to develop and commercialize in exchange for payment of milestones and ongoing royalties to Mylan based on net sales of the products. Specific product and financial details were not disclosed.

"Building strategic alliances of this type for MTI is consistent with the growth and brand re-entry strategy that we previously outlined," said Robert J. Coury, Mylan's Vice Chairman and Chief Executive Officer. "This type of collaboration will leverage MTI's state-of-the-art technology and expertise and has the potential to allow Mylan to participate in branded commercial opportunities without additional R&D net costs. These agreements are the latest in what we believe will be a series of branded strategic alliances and further demonstrate MTI's position as partner of choice for transdermal technology."

Mylan Laboratories, Inc., is a leading pharmaceutical company with three principal subsidiaries, Mylan Pharmaceuticals, Inc., Mylan Technologies, Inc., and UDL Laboratories, Inc., that develop, license, manufacture, market, and distribute an extensive line of generic and proprietary products.

Endo Pharmaceuticals Announces License Agreement With ZARS for Synera, An FDA-Approved Topical Local Anesthetic Patch

Endo Pharmaceuticals Inc., a wholly owned subsidiary of Endo Pharmaceuticals Holdings Inc., recently announced it has signed a license agreement with ZARS Pharma that will give Endo the exclusive North American rights to Synera (lidocaine 70 mg and tetracaine 70 mg) topical patch. Under the terms of the agreement, Endo will pay ZARS an upfront fee of $11 million, with additional payments of up to approximately $27 million upon achievement of certain commercial milestones. Endo will also pay ZARS undisclosed royalties on net sales of Synera. ZARS is a privately held company based in Salt Lake City, Utah, focused on the development and commercialization of patented technologies that deliver drugs into and across the skin.

Synera is a topical local anesthetic patch for use on intact skin to provide local dermal analgesia in children and adults. Approved by the US FDA on June 23, 2005, Synera is expected to become commercially available in the second half of 2006. The safety and efficacy of Synera have been demonstrated in a series of clinical trials that included more than 660 pediatric (aged 3 to 17 years) and adult patients undergoing superficial dermatological procedures.

"We are pleased to add an innovative treatment, such as Synera to our growing product portfolio," said Peter A. Lankau, Endo's President and Chief Executive Officer. "We believe that Synera is a good strategic fit for Endo, consistent with our objective of expanding our commercial presence in the institutional setting."

He noted that Endo will promote Synera through its existing 70-person hospital sales force, which currently promotes DepoDur (morphine sulfate extended-release liposome injection), a novel single-dose, extended-release injectable formulation of morphine.

According to published data, children under the age of 15 are hospitalized for an estimated 11.5 million days annually. These children are routinely subjected to multiple venous access procedures, such as, IV starts, IV changes, and blood draws.

Mr. Lankau added that Synera will also be studied for use with additional procedures, such as pediatric immunization, potentially giving healthcare providers another option to reduce the injection-site pain associated with childhood immunizations.

Synera has a thin layer of local anesthetic formulation integrated with an oxygen-activated heating element (Controlled Heat-Assisted Drug Delivery, or CHADD). The heating element enhances the delivery of lidocaine and tetracaine anesthetics into the skin. When removed from the storage pouch, the patch begins to heat, warming the skin after application. Synera has a familiar, adhesive bandage-like appearance and is applied 20 to 30 minutes prior to venipuncture, intravenous cannulation, or superficial dermatologic procedure.

Attorney REVIEW

Preparing For Drug Pedigrees

By: Kendra Martello, Esq.

BIOGRAPHY

Ms. Kendra A. Martello is an attorney in the FDA Practice Group of Heller Ehrman LLP in Washington, DC. Her practice focuses on FDA regulatory, compliance, and enforcement issues pertaining to pharmaceuticals (prescription and OTC), medical devices, biotechnology, dietary supplements, and food, including FDA and FTC regulation and enforcement in matters involving drug advertising. She also regularly counsels clients on Drug Enforcement Administration (DEA) and Federal Trade Commission (FTC) regulation and oversight of drug manufacturers and distributors, as well as on consumer product regulation and enforcement matters before the Consumer Product Safety Commission (CPSC). Ms. Martello also has extensive experience in negotiating and drafting clinical trial and other FDA-related agreements on behalf of drug and medical device manufacturers.

Drug counterfeiting has become a significant problem in the United States. According to recent statistics from the Center for Medicines in the Public Interest, the volume of counterfeit drug sales is projected to reach $75 billion by 2010. As a result, federal and state governments are developing "pedigree" requirements that aim to trace the movement and ownership of prescription drugs to detect and prevent counterfeiting. These requirements, some of which are set to become effective this year, will have a potentially significant impact on drug manufacturers, wholesalers, and other distributors, and such companies should be proactively preparing to meet the pending pedigree requirements. This column summarizes the pending federal rules, and those being implemented in Florida and California.

To combat drug counterfeiting, many states have developed "pedigree" requirements that will track a drug product from the manufacturer to the end customer or some portion of the drug distribution chain. The Food and Drug Administration (FDA) also promulgated rules to track wholesale distributions of drug products; however, these rules have been repeatedly stayed and currently are not scheduled to take effect until December 1, 2006. While other states have implemented and/or considered pedigree requirements, Florida's and California's are two of the most significant. Additionally, state legislative reforms aimed at curbing drug counterfeiting typically include additional measures to exercise controls over wholesale drug distribution generally (eg, bond or equivalent security requirements, designated representatives, increased licensure or registration requirements). This article is limited to the pedigree components of such legislation.

FEDERAL LEGISLATION

The Prescription Drug Marketing Act (PDMA), first passed in 1987, requires pedigrees for prescription drug products in the chain of distribution. Specifically, the Act requires each person engaged in wholesale distribution of a drug, *who is not the manufacturer or authorized distributor of record* of such drug, to, before each distribution, provide the person receiving the drug with a statement identifying each prior sale, purchase, or trade of such drug (including the date of the transaction and the names and addresses of all parties to the transaction).

The FDA promulgated regulations implementing these PDMA pedigree requirements; however, the effective date of the regulations has been repeatedly postponed. Most recently, the FDA stayed the effective date until December 1, 2006, on the grounds that it wanted to provide industry time to voluntarily implement electronic pedigree technologies, which the Agency anticipates may be accomplished by 2007. As the Agency explained in 2004, the FDA is working with stakeholders

through its counterfeit drug initiative to facilitate widespread, voluntary adoption of track and trace technologies that will generate a de facto electronic pedigree, including prior transaction history back to the original manufacturer, as a routine course of business. If this technology is widely adopted, it is expected to help fulfill the pedigree requirements of the PDMA and obviate or resolve many of the concerns that have been raised with respect to the final rule by ensuring that an electronic pedigree travels with a drug product at all times.

Most recently, the FDA announced a public meeting to be held on February 8-9, 2006, to discuss anti-counterfeiting issues generally and to include vendor displays of radiofrequency identification (RFID) technology as a mechanism to combat drug counterfeiting. The meeting notice acknowledges continued concerns regarding the feasibility of widespread RFID implementation by December 1, 2006. The meeting is intended to solicit public comment on whether the FDA should continue to delay the effective date of its pedigree requirements, let the regulatory requirements become effective, or take other action, as well as other significant issues.

FLORIDA STATE REQUIREMENTS

While the FDA continues to postpone implementation of its proposed rules and evaluate the feasibility of drug pedigrees, Florida and California have separately developed drug pedigree legislation that will take effect in 2006 and 2007, respectively.

Under Florida law, effective July 1, 2006, each person engaged in the wholesale distribution of a drug product, *who is not the manufacturer,* must, before distribution of the drug, provide the person who receives the drug with a pedigree paper. Unlike the PDMA, there is no exemption for "authorized distributors of record." Moreover, the Florida statute clearly states that repackagers must comply with pedigree paper requirements. A repackager is any person that repackages a product; "repackage" is defined as repacking or otherwise changing the container, wrapper, or labeling to further the distribution of the drug. To verify compliance, each manufacturer must make available, upon request, distribution documentation related to its sales of prescription drugs.

A "pedigree paper" is defined as a document in written or electronic form, approved by the Florida Department of Health, containing information that records each distribution of a legend (ie, prescription) drug, from sale by a pharmaceutical manufacturer through acquisition and sale by any wholesaler or repackager, until final sale to a pharmacy or other person administering or dispensing the drug. The pedigree paper must detail:

- the drug name and the manufacturer's name;
- the amount of the drug;
- its dosage form and strength;
- its lot number;
- the name and address of each owner of the drug and his signature;
- shipping information, including the name and address of each person certifying delivery or receipt of the drug;
- an invoice number or a shipping document number or another number uniquely identifying the transaction;
- a certification that the recipient wholesaler has authenticated the pedigree papers; and
- the name, address, telephone number, and, if available, the email address for each wholesaler involved in the chain of custody of the legend drug.

Thus, the Florida statute allows the pedigree to be either in paper or electronic form. If the pedigree is stored in electronic form, the electronic record must be easily readable or easily rendered into a readable format, and capable of being produced onto paper. Data in an electronic pedigree may also be transmitted via the Internet, CD-ROM, smart card, or other similar devices.

In a "Questions and Answers" document released by the Florida Bureau of Statewide Pharmaceutical Services, the state clarifies that if a manufacturer engages in wholesale distribution of a drug that it did not manufacture, then a pedigree paper is required. A manufacturer is not, however, required to provide a pedigree paper when it sells or distributes a product that it manufactures. In the Questions and Answers document, the state clarifies that a manufacturer includes the actual manufacturer, the NDA/ANDA holder even though a contract manufacturer is used, and it includes the distribution point for the manufacturer whether the distribution point is owned by the manufacturer or is a contracted third-party logistics provider for a manufacturer. If a manufacturer also engages in the wholesale distribution of any prescription drug that it did not manufacture, then a pedigree paper is required to be provided to the recipient of the drug.

Wholesale distributors are required to authenticate each transaction on a pedigree paper, using one or more of the following means:

- receipt of an invoice or other shipping document from the seller to the purchaser. If this mechanism is used, the wholesaler must review the document for signs of tampering, incompleteness, or inconsistency as compared to other invoices or shipping documents from that manufacturer or wholesaler, and must randomly verify the authenticity of the invoice or shipping document with the seller or shipping point reflected on the document;
- telephone call to the seller;

- e-mail communication to the seller;
- verification of the transaction through a web-based system established by the seller or an independent secure third party;
- receipt of a legible and unaltered copy of a previous transaction's pedigree paper that had been signed under oath at the time of the previous transaction to support the transaction to which the pedigree paper relates; or
- receipt of a pedigree in electronic form.

If a pedigree paper cannot be authenticated due to a clerical error, it must corrected by the sender. If it cannot be authenticated for a reason unrelated to a clerical error, or the reason cannot be satisfactorily determined based on a preliminary investigation, the shipment must be quarantined and the state notified within 3 business days.

Wholesale distributors also must annually provide the state with a written list of all wholesale distributors and manufacturers from whom the wholesaler distributor purchases drugs, and notifications of any changes to the list must be made not later than 10 days after any change to the list. A proposed compliance policy to extend the initial enforcement date for pedigree papers for generic drugs until January 2007 has been released; however, it has not been adopted as of the time this column was written, and it is difficult to predict whether it will ultimately be adopted. The proposal will undoubtedly gain support among some drug manufacturers; however, some may seek to implement pedigree papers earlier to gain a competitive advantage.

CALIFORNIA STATE REQUIREMENTS

California's pedigree legislation is perhaps the most comprehensive in that it requires manufacturers to initiate a drug pedigree, and it requires that all pedigrees be provided in electronic form. A pedigree in California must document each change in ownership of the drug, beginning with the manufacturer through to the pharmacy or other person dispensing, furnishing, or administering the drug. Again, unlike the PDMA, California law does not recognize the concept of "authorized distributors of record."

A pedigree in California must include:

- the source of the drug, including the name, address, state license number, and, if available, California state license number of the source;
- the quantity of the drug, its dosage form and strength, the date of the transaction, the invoice number, the container size, the number of containers, the expiration dates, and the lot numbers;
- the business name, address, and, if appropriate, the state license number, including California state license number, of each owner of the drug, and the drug's shipping information, including the name and address of each person certifying to delivery or receipt of the drug; and
- a certification from a responsible party of the source that the information in the pedigree is true and accurate.

To date, California has not developed regulations to implement these requirements. The legislation is currently slated to take effect on January 1, 2007; however, a statutory mechanism exists to extend the implementation date until January 1, 2008, if the California State Board of Pharmacy determines that manufacturers or wholesalers require more time to implement electronic technologies to track drug products. It is difficult to predict whether implementation of these requirements will be stayed, and thus, manufacturers should be preparing for such implementation.

SUMMARY

Some significant differences exist between the California and Florida requirements previously discussed. While Florida clearly states that a pedigree can be either paper or electronic, California's law clearly mandates the use of electronic pedigrees. Additionally, Florida's pedigree requirements initiate with the first wholesale distribution of a drug product; on the other hand, California will require manufacturers to initiate the pedigree. Finally, returns are not required to have a pedigree in Florida, while all changes in ownership, including returns, will require a pedigree in California.

At the same time, the FDA is closely monitoring these developments, as evidenced by its re-establishment of its Counterfeit Drug Task Force and its continued public meetings. The possibility exists that if state requirements become too stratified and/or manufacturers or distributors appear too slow to implement electronic pedigree systems, the FDA may step in and attempt to create a national standard. Voluntary industry efforts may also be forthcoming. Even if a national standard does not occur, it is clear that the distribution of prescription drugs is changing, and the use of pedigrees is an important consideration for all parties in the distribution chain to help protect against drug counterfeiting.

Companies who may be affected by the pending pedigree requirements should already be preparing for compliance. Given the complex, and potentially inconsistent requirements of the various pending rules, questions may inevitably arise for which companies can contact the author for guidance. ♦

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A Decade in Review: The Evolution of the Drug Delivery Industry

By: Debra Bingham and Christopher Robinson, PhD, MBA

BIOGRAPHIES

Ms. Debra Bingham is a Founding Partner of Valeo Partners, a Washington, DC-based consultancy that provides strategic consulting and business development services to life science companies in the pharmaceutical, biotechnology, medical device, and drug delivery markets. As part of the Valeo team, Ms. Bingham brings clients over a decade of specialized expertise in the area of drug delivery, specialty pharmaceuticals, and generic businesses, as well a deep understanding of the key technologies and market play. At Valeo, her primary focus is in helping clients in the areas of business strategy, business development, growth opportunity assessment, and strategic partnering. She also leads Valeo's strategic partnering offering in affiliation with Stonecroft Capital, a DC-based investment bank, which provides full-service transactional capabilities from licensing to M&A. Prior to joining Valeo, Ms. Bingham spent the majority of the past 10 years working in the pharmaceutical industry assisting companies with strategic business assessment and business development. She has authored many drug delivery business articles and technology reviews and is a featured speaker at industry trade conferences. She also worked for an international consulting company and before that held a scientific research position. Ms. Bingham is an active member in the Licensing Executive Society, the Controlled Release Society, and the American Association of Pharmaceutical Scientists.

Dr. Christopher Robinson is a Founding Partner of Valeo Partners, a Washington, DC- based consultancy that provides strategic consulting and business development services to life science companies in the pharmaceutical, biotechnology, medical device, and drug delivery markets. At Valeo, Dr. Robinson's primary focus is in helping clients develop winning business strategies, generate innovative product concepts, evaluate market opportunities, and optimize portfolio strategies. He brings a results-oriented philosophy to traditional strategic consulting, and has extensive experience working with executive management and cross-divisional project teams to turn strategy into proven results. Prior to joining Valeo, Dr. Robinson was a Management Consultant at a global strategy consultancy focused on product development strategy, business process optimization, and implementation. He earned his MBA from Cornell University with specialization in venture capital and entrepreneurship and a PhD in Immunology from the University of Florida where he focused on autoimmune disease and genomics. He also holds a BS in Molecular Biology from Lehigh University.

The global drug delivery industry has grown from just under $20 billion in product revenue in 1995 to nearly $70 billion today (Figure 1). Drug delivery has gone from a niche business to a well-established and important segment of the pharmaceutical industry. It is accepted as an essential life-cycle management tool and an enabling instrument for many key pharmaceutical products, such as Lupron Depot®, Zyprexa® Zydis®, Wellbutrin XL®, and Duragesic®. While the market acceptance of drug delivery products has faired very well for many technology providers, the changes in the pharmaceutical industry as a whole have placed a strain on the traditional drug delivery business model. Consolidation in the pharmaceutical industry, thinning pipelines, and the growth in the generic industry (Figure 2) has greatly impacted drug delivery companies throughout the past decade.

The traditional drug delivery business model is completely reliant on the drug delivery company's ability to sign licensing deals for the use of its proprietary technology with partner molecules. Success depends on the quality of the partner molecule and the partner's ability to adequately market the product. In the mid 1990s, drug delivery companies began to amass technology, because at the time, it was believed that attracting a large platform deal would be more likely with a wealth of technology options (Table 1). This was not the case. Even with broad and varied platform technologies, drug delivery companies were not able to produce the expected growth in revenue through early stage licensing deals. In order to grow and produce substantial revenues, the companies recognized the need to make fundamental changes to the "pure play" drug delivery business model.

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[i] Wiess, P.M., http://www.femalepatient.com/html/arc/sig/pharma/articles/028_07_031.asp
The dual chamber cartridge shown is a Vetter Lyo Cartridge (V-LK®).
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TABLE 1

VALEO PARTNERS

Expanding the Offering

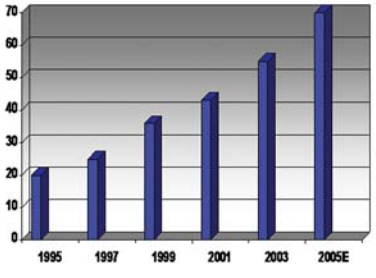
Company	Acquisition
Alkermes	Enzytech, Medisorb, AIR
Aradigm	Weston Medical
Cephalon	CIMA
Elan	Sano, Dura, TLC, Athena, Nanosytems
Nektar	Bradford, Shearwater, Aerogen
Watson	TheraTech
SkyePharma	Jago, DepoTech, Hyal, RTP, Bioglan

Source: Valeo analysis, company annual reports

FIGURE 1

VALEO PARTNERS

Market Growth 1995-2005



- In 1995, the majority of the revenues were produced by Oral CR/DR, followed by inhalation, and transdermal products.
- In 2005, the majority of the revenues were produced by, SR depots/implants, PEGylated products, oral CR/DR, and inhalation products.

Source: Valeo analysis, Annual reports, MedAd News, IMS

CONSOLIDATION & THE RISING OPPORTUNITY

From the mid-1990s, consolidation in the industry made partnering with big pharma more difficult and more risky for the drug delivery company. As the industry consolidated both in the branded and generic sectors, drug delivery companies had fewer potential partners with large life-cycle management and development budgets. Just a sampling of the major consolidation that took place throughout the past decade:

- Pharmacia AB and The Upjohn Company merger 1995
- Sandoz and Ciba merger 1996
- Glaxo Wellcome and SmithKline Beecham merger 2000
- Pharmacia & Upjohn and Monsanto/Searle merger 2000
- Pfizer and Pharmacia merger 2000
- Pfizer and Warner Lambert merger 2003
- Sanofi-Synthelabo and Aventis merger 2004
- Yamanouchi and Fujisawa merger 2004

As with any significant change in the marketplace, there are winners, and there are losers. The consolidation in the industry has created both. The winners include a number of drug delivery companies that have been able to capitalize on the shift by adjusting business strategy in such a way to take advantage of the vacuum that is created in the market as it consolidates. As an example, companies such as Biovail, and Alkermes are successfully transitioning from technology licensing toward product development and marketing.

While the consolidation in the pharmaceutical market caused many drug delivery companies heartache, it is what ultimately opened up great opportunity for a number of small savvy companies. Merged pharmaceutical companies began to divest smaller or duplicative products, which became available for specialty pharma and drug delivery companies. Moreover, because large pharma require multiple, blockbuster drugs to reach double-digit growth on an annual basis, smaller or niche markets are left untouched. This opens up product opportunities in the market where there is relatively little competition. In most cases, large pharma will not consider developing a product that does not have peak

FIGURE 2

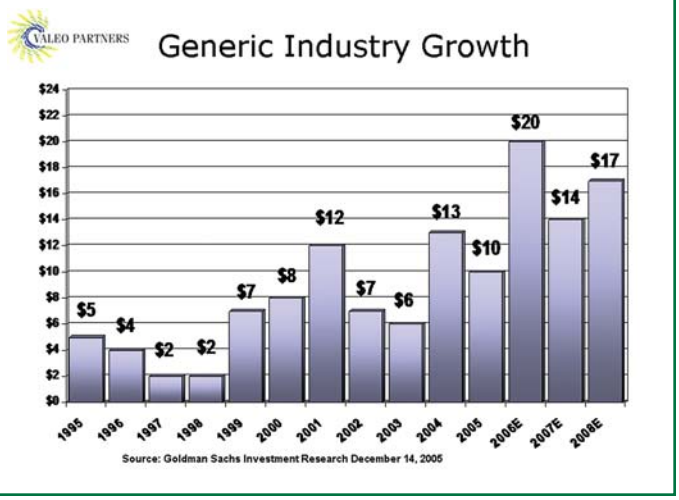
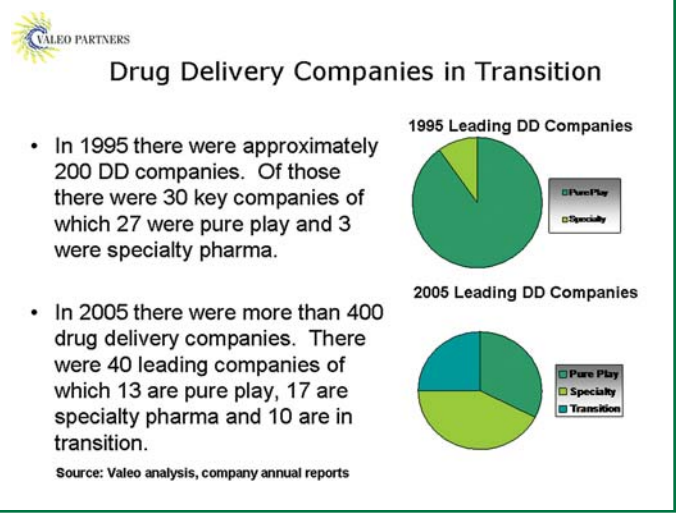


FIGURE 3



sales potential of over $500 million. There is a lot of room for market entry under $500 million. With this opening in the market, drug delivery companies were able to use creative product concept design and proprietary technology to develop some very strong specialty pharmaceutical products. Endo Pharmaceuticals has taken advantage of the market dynamics and has in-licensed rights to late-stage specialty products from drug delivery companies that have made the transition to product development.

In 1995, there were approximately 200 established drug delivery companies. The vast majority of these companies claimed to be pure play drug delivery companies and did not develop products without sponsorship from big pharma. The key players in 1995 included ALZA, Alkermes, Elan, Jago, and Noven among others. By 2005, the number had grown to over 400 companies, and many of the top companies had internal development projects underway (Figure 3).

Comparing 10 drug delivery companies that were strong in 1995 with their standing in 2005, highlights the trend toward integration. Of the 10 companies, 5 have been acquired by other drug delivery companies or pharmaceutical companies, 3 are specialty Pharma, and 2 are in transition (Table 2). The majority of publicly traded drug delivery companies have openly stated that the business plans now include product development on some level (Table 3).

DRUG DELIVERY PRODUCTS

Business models are not the only important indicator of change in the industry. It is interesting to look at how drug delivery products have evolved as well (Figure 4). It was thought that drug delivery would move earlier into the pipeline of big pharma companies and would be more often employed with Novel Molecular Entities (NMEs). There is little evidence that this has come to pass. There are some examples of NMEs that were first launched with advanced drug delivery technology, but this is the exception rather than the rule. The majority of drug delivery products approved throughout the past 10 years are examples of life cycle management of an already approved product (Figure 5).

As many of the leading drug delivery products are coming off patent, large generic companies are partnering or acquiring the needed drug delivery

TABLE 2

VALEO PARTNERS

Where are the Players from 1995?

Company (technology focus)	BM '95	BM '05
Alkermes (SR depot, BBB technology)	Pure play	Specialty
ALZA (oral CR, transdermal)	Pure play	Big Pharma
Biovail (oral CR)	Pure play	Specialty Generic
Cygnus (transdermal)	Pure play	J&J acquired TD
Elan (oral CR)	Pure play	Transition
Jago (oral CR)	Pure play	SkyePharma
Inhale Therapeutics (pulmonary delivery)	Pure play	Nektar in transition
Noven (transdermal)	Pure play	Specialty
R.P. Scherer (orally-disintegrating, soft gels)	Pure play	Cardinal
TheraTech (transdermal, oral transmucosal)	Pure play	Watson

Source: Valeo analysis, company annual reports

TABLE 3

VALEO PARTNERS

Drug Delivery Then & Now

Company	12/29/95	12/30/05	Company	12/29/95	12/30/05
APS	5.50	1.53	Emisphere	6.75	4.34
Alkermes	7.94	19.12	Fuisz	10.17	Acquired
ALZA	24.50	Acquired	Nektar	9.75	16.46
Andrx	16.13 (96)	16.48	KV	8.92	20.60
Anesta	9.25	Acquired	Kos	15.00 (96)	51.73
Aradigm	9.88 (96)	.73	TLC	20.00	Acquired
Atrix	7.75	Acquired	Matrix	18.75	Acquired
Biovail	25.75	27.53	NeXstar	16.25	Acquired
CIMA	6.00	Acquired	Noven	11.25	15.13
Columbia	9.00	4.65	Penwest	8.44 (97)	19.52
Cygnus	22.38	Acquired	Sequus	14.25	Acquired
DepoTech	19.25	Acquired	SkyePharma	11.48 (97)	8.53
Dura	17.38	Acquired	SuperGen	12.25 (96)	5.05
Elan	24.31	13.93	TheraTech	12.00	Acquired

Source: NYSE

TABLE 4

VALEO PARTNERS

Top 20 DD Products 1995 & 2005

Product Name 1995		Product Name 2005	
Lupron Depot	Proventil MDI	Prevacid	Protonix
Procardia XL	K-Dur	Nexium	Toprol XL
Cardizem CD	Vancenase	Advair	Aciphex
Prilosec	Estraderm	Effexor XL	Flovent
Zoladex	Calan SR	Neulasta	Flonase
Serevent MDI	Claritin-D	Lupron Depot	Pulmicort
Ventolin MDI/DPI	Azmacort MDI	PEGASYS	Ortho Evra
Pulmicort DPI	Adalat CC	OxyContin	Paxil CR
Atrovent MDI/DPI	Beconase AQ	Duragesic	Wellbutrin XL
Depo-Provera	Seldane-D	Prilosec	Depakote

Source: Valeo analysis, Rxlist.com, MedAd News

technology to launch equivalent products. Many of the key drug delivery products of 1995 are now available as generic products (Table 4). The leading generic companies such as Sandoz, TEVA, and Mylan, have strong internal drug delivery capabilities, and are willing to partner with or acquire other companies to gain the needed technology. This was not the case, throughout the 1990s. Most drug delivery companies were not able or willing to license technology to the generic industry, and generic companies were not interested in paying upfront payments and royalties. Currently, as major branded drug delivery products come off patent, generic companies have the internal drug delivery technology either through acquisition or partnerships to successfully launch generic versions. Furthermore, many generic companies are interested in a branded play and understand that drug delivery technology is important to the development of strong, branded products that offer market differentiation.

While a decade in the life cycle of any industry is an extraordinarily short time in the big picture it is clear that a decade can make a very big difference regarding specific companies and products, especially in this industry. The drug delivery industry was mainly in a growth cycle for more than 30 years in product sales and in numbers of start-up companies. Beginning in the late 1990s, the drug delivery industry felt some growing pains from increased competition and the reliance on big pharmaceutical companies (Figure 6). The traditional drug delivery model was beginning to

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

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FIGURE 4

FIGURE 5

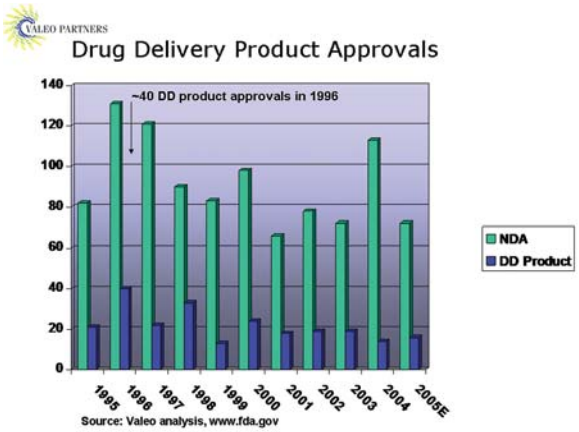
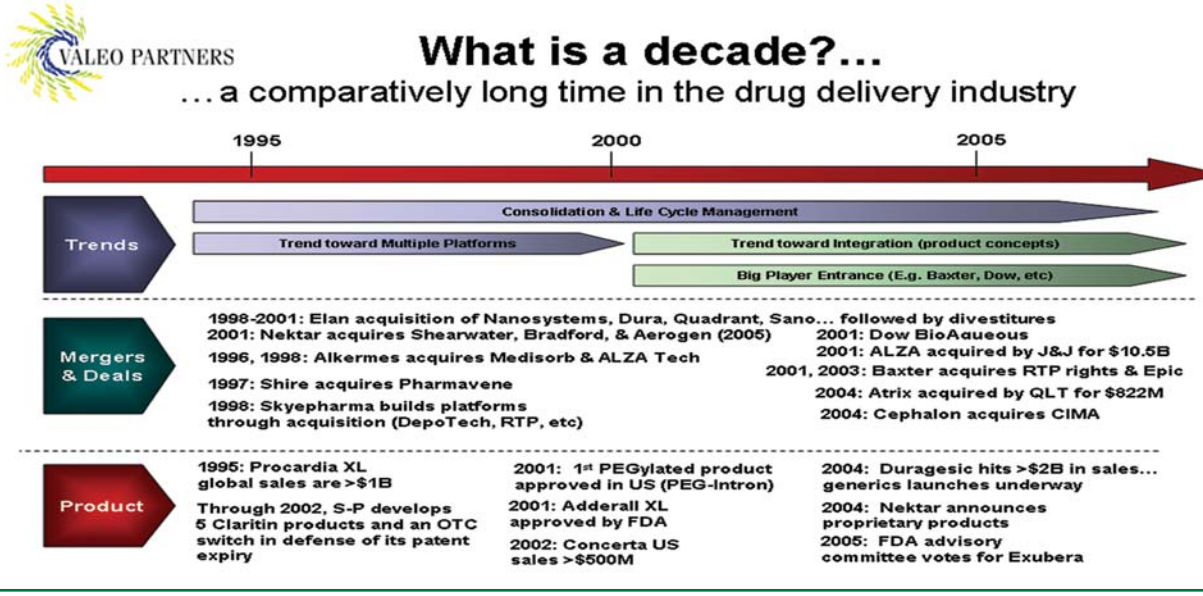


FIGURE 6



show signs of failure. Wall Street and industry leaders began to question the wisdom of complete reliance on big pharma for revenue and growth.

Now, it is expected that the drug delivery market will continue to grow into the next decade as a number of key products are expected to launch. There are drug delivery products under development that are expected to be extremely successful throughout the next 5 to 10 years, including Exubera® (Pfizer/Nektar) and others. *Editor's note: at press time, Pfizer had acquired the rights to Exubera from Sanofi-Aventis for $1.3 billion.* Big pharma, biotech, and generic companies will continue to acquire and develop key technology. Drug delivery business models will continue to evolve as the market matures; however, there will remain a need for drug delivery companies with well-defined, deep expertise. ♦

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EXCIPIENT UPDATE

Medical Propellant Manufacturing: A Decade of Leadership

By: Tim Noakes, PhD, and Mark O'Sullivan

INTRODUCTION

Metered dose aerosol inhalers (MDIs) have been used for drug delivery to treat pulmonary disease for many years. Historically, the propellants used were chlorofluorocarbons (CFCs), but in response to the requirement to phase these out under the provisions of the Montreal Protocol, formulations using hydrofluoroalkane (HFA) propellants have been introduced, and the proportion of HFA to CFC MDIs is steadily increasing.

MDIs containing HFA propellants began to be developed during the early 1990s, and in October 1995, the world's first stand-alone medical propellant plant was commissioned at INEOS' (then ICI) Runcorn, UK, facility to make medical-grade HFA 134a. This represented a fundamental break with the past, as previously propellants for medical uses had been produced and finished on the same equipment that made technical grades of the gas.

That first pharmaceutical grade 134a plant is now 10 years old, and the Montreal Protocol is approaching its 18th birthday. This article, will detail the continuing improvements and changes in the medical propellant manufacturing industry since that plant was commissioned, and some of the issues that have had to be resolved.

HFA 134A: THE CFC REPLACEMENT

Almost 50 years of CFC-powered MDIs has given the pharmaceutical industry and its end users (the patients) a high degree of confidence in their safety and efficacy. Replacing CFCs was always going to be a difficult task, and in the end, only two propellants appeared to be suitable, HFA-134a and HFA-227ea.

The bulk of material delivered to the lungs by an MDI is, of course, the propellant, which can amount to 99.9% of the emitted formulation. This, coupled with the potential daily use over many years by a patient, and the fact that neither of these propellants had ever been used in medical applications, caused the regulatory authorities to be naturally cautious about their use.

It soon became clear that they would require these new excipients to be rigorously tested, manufactured, and controlled to the same standards as a new drug. This approach was, until then, almost unheard of, presenting the propellant manufacturers with considerable challenges in order to meet these requirements.

A NEW TYPE OF PLANT

Existing CFC propellants were supplied from refrigeration-grade plants, with varying degrees of extra controls applied under what amounted to a "batch picking" regime. INEOS was the first to reject this traditional approach as being unsuitable for manufacture of the new

FIGURE 1

INEOS' ZEPHEX Plant

HFAs in the developing regulatory climate of the 1990s. It was clear that only a separate, dedicated pharmaceutical-grade HFA-134a facility that was fully validated and complied with the requirements of the current Good Manufacturing Practice (cGMP) guidelines would be appropriate. The plant that INEOS Fluor constructed at Runcorn, opening in late 1995, was the world's first such medical propellant "polishing" facility, taking refrigerant-grade 134a and purifying it further under rigorous conditions to produce a high-purity medical grade.

NOT ONLY A PLANT

A modern medical propellants offering is composed of much more than just the production asset. State-of-the-art analytical methods, often specifically developed and validated for the application, are critical. These methods must be able to detect the full sweep of potential 134a impurities, not only of that manufacturer (which would have been a much easier task for INEOS as it's 134a only contained a few), but of all other suppliers, as it is important that a supplier can always prove the absence of other impurities to the regulatory authorities.

At INEOS, this led to the development of a suite of new methods, capable of detecting all possible 134a impurities down to levels typically of 1 ppm or less. In addition to the multimillion dollar gas chromatography method, care must also be taken over the more mundane but critical tests – non-volatile residue (a test for oil & grease), odor, and moisture.

A further, new requirement was for stability data. CFCs having been in use for many years, had had their stability convincingly demonstrated "in the field" without formal stability studies of the propellant, and in fact, they have been used for such a long time that their use predated any regulatory requirements for such data.

However, as a new propellant, data on the stability of HFA-134a was clearly required, and all manufacturers have had to carry out extensive stability trials on these propellants. In one sense, this was a little bizarre, as parallel "technical" data in the refrigeration use of technical grades of these propellants provides ample evidence that they are stable up to temperatures of hundreds of degrees Celsius, but as the data was usually not from a GMP study, it could not be included in regulatory submissions. INEOS now possesses 5-year GMP data for these propellants at elevated temperatures.

INSPECTION

Regulatory inspections of propellant manufacturing facilities tend to vary, depending on what country they are based in and what markets they are supplying. Within the EU, Bulk Pharmaceutical ingredient (BPC) manufacturers are not

FIGURE 2

An Inside Look at the Company's Lab

automatically inspected. However, regulatory authorities tend to view these critical propellants, which are inhaled into the lung every day, in some cases for life, as Active Pharmaceutical Ingredients (APIs). INEOS has firmly embraced this view and by being under the jurisdiction of the UK MHRA, is able to volunteer for a regular inspection program where its GMP is assessed against the ICH GMP guidelines applied to APIs. INEOS gained approval for ZEPHEX 134a in August 2000, shortly after the scheme started, and ZEPHEX 227 in September 2001.

CHANGING STANDARDS

Successful commissioning of a medical propellants purification plant is only the start, however. Back in 1995, INEOS worked to what were then the latest standards, but it is amazing now to look back and see how much things have moved on as time has gone by.

In 1995, the focus was to deliver a facility compliant with GMP at that time. But to remain compliant, a vigorous program of continuous improvement is required to keep up with the ever-progressing requirements of cGMP. As a leader in its field, INEOS Fluor's active strategy is to continually drive new standards forward, rather than in any sense be dragged along by events, regulatory or otherwise. This has led to improvements in procedures in many areas; from documentation, through package control to data handling.

A BUSY LAB

Due to the trace amounts of impurity being removed, today's pharmaceutical-grade HFA plant design requires monitoring of performance by in-process analysis, rather than by monitoring plant variables. This integral reliance on analysis as part of processing generates a high volume of samples for the QC Laboratory.

In the case of a busy facility, such as INEOS', this makes the case for the introduction of a fully validated Laboratory Information Management System (LIMS) into the laboratory, which frees analysts from part of the chore of data checking and provides numerous other benefits, including leading to even higher levels of cGMP.

THE BENEFIT OF LIMS

The use of LIMS has resulted in significant improvements to sample workflow, laboratory throughput and control of raw data, and reduction in manual data handling errors. A LIMS allows tracking of all samples received into the laboratory, all tests performed and results generated, compliance with specifications etc, and to produce reports based on the results generated. LIMS systems have been in existence since the 1970s, but it is not until relatively recently that the technology was considered mature enough to install and validate such a system.

The current generation of LIMS includes client/server systems integrated into the desktop PC Windows environment. Some of the current systems have been designed from the ground up with cGMP and CFR21 Part 11 compliance in mind. In 2002, INEOS Fluor chose LabWare as its LIMS provider. A joint project to install and validate LabWare LIMS was extremely successful and resulted in a robust installation of this industry-standard software package.

PRODUCT QUALITY

It takes time and experience that can only be gained by extensive production for a manufacturer to really fine-tune a purification process, so over time, there has been a tendency for specifications to tighten as companies learn the optimum operating conditions for their plants. With INEOS, this has resulted in some of the tightest propellant specifications in the world.

EXPANDING THE SCOPE

In the days of CFC supply, a "medical" propellant manufacturer believed it had fulfilled the contract when the product was delivered to the user. Nowadays, this is just one part of a wide-reaching package of assistance and support it is expected and willing to give. This covers many aspects but includes engineering support in propellant handling, acceptance testing via an independent contractor, which relieves the end user of much of that chore, and a highly responsive logistics and transport system.

This last characteristic may seem a little mundane, but is in fact crucial to efficient use of the new HFAs. Most users (because of the technical sophistication of the propellants) are very nervous about multiple sourcing, and are often restricted by regulatory arrangements as well. In consequence, a good On Time in Full (OTIF) performance by a propellant supplier ceases to be a luxury and becomes a necessity. Certainly, at INEOS, this is one on a number of quality metrics that are watched very closely.

THE FUTURE

If the past 10 years have taught the propellant supply industry anything, it's that standards do not stand still, and HFA MDI propellants are a long way from being mature. Looking in INEOS' crystal ball, all sorts of interesting possibilities can be seen, some which can only be shared with customers, and some of more general interest.

It can be expected that the drive to tighten specifications will continue, although the emphasis will move away from "9s Chasing" on the related impurity clauses, though lowering limits of detection may still make this a challenging area of Quality Control. The focus is already switching to apparently basic, but critical, requirements like odor and particulate content control. Suppliers will be expected to ensure that propellant, even though some of the assets that handle it belong to the MDI manufacturer, arrives at the filling turret in the condition it was when made.

It must always be remembered that these propellant gases are taken, in relatively large amount, into the often-compromised respiratory tract of a patient for life. As such, it is INEOS' view that only the best is acceptable for both the manufacturing and handling of these products, and that a good comparison, for care, control, and rigor would be water for injections.

BIOGRAPHIES

Dr. Tim Noakes trained as an organic fluorine chemist at Manchester University, UK, in the 1970s. He joined ICI in 1975 and has since worked on a wide range of technical projects, spanning chemistry, laser technology, electrostatics, and crop protection; with an emphasis on atomization science and technology. In 1989, he joined the HFAs business of ICI and became deeply involved in the technical aspects of the CFC/HFA transition from a medical propellant supply standpoint and has since become a recognized international expert on the subject. In early 2001, ICI sold its fluorocarbon business to the INEOS group, where it became INEOS Fluor, and today, he is the techno/commercial leader of the INEOS Fluor medical propellants business. He is based at Runcorn in the UK, near Liverpool.

Mr. Mark O'Sullivan is a graduate of the Royal Society of Chemistry and is the leader of the INEOS Fluor propellant analytical laboratories in the UK. He was key in establishing the QC laboratory when the new medical 134a plant was constructed at Runcorn, and since then, has been a leading contributor to the refinement of the quality of the INEOS Fluor medical propellants offering. He has expertise covering a wide swathe of analytical techniques from state-of-the-art gas chromatography through to moisture determinations.

REVISITING INTRALESIONAL DELIVERY OF CANCER TREATMENT

By: Craig Dees, PhD

INTRODUCTION

Methods used to treat cancer are still relatively primitive. The technologies have gained in sophistication and complexity, but the underlying premise and results remain much the same as performed many years ago. Let's call this approach "high-tech primitive." The leading high- tech primitive option, and the one that has the most chance of success in cancer treatment, is surgical removal of the lesion. Sadly, the side effects of excision may be horrific and include mutilation or loss of organ function.

The focus of surgery is to save life, while any collateral damage is expected to be accepted by a grateful patient whose life has been saved. An example of this was driven home to me several years ago after giving a presentation on new methods to reduce the side effects of breast cancer treatment. I was approached by a young breast surgeon who said to me, "I don't understand the need for new breast cancer treatments when I can cure 97% of my patients now [using radical mastectomy]." I asked if her patients were pleased with the loss of one or both breasts. She reacted in shock and surprise, as though this was a new thought about the quality of the patient's life after her work. She grudgingly responded, "I guess they aren't."

Anyone can look at a variety of Internet sites on lumpectomy and see results that the surgeon says are cosmetically acceptable. Take the same set of pictures and ask a group of women and you will get the exactly opposite opinion. Similarly, I have heard similar comments voiced by physicians who treat prostate cancer, and got the same shocked responses when I asked about their patients' quality of life.

Fortunately, the attitude that saving the patient's life is the only thing that counts is finally going out of fashion. Renewed efforts are being made to improve quality of life by refining surgical procedures and implementing tissue-sparring approaches like lumpectomy for breast cancer. New tissue-sparring endpoints for licensure of treatments by the FDA are adding momentum to novel cancer treatments that reduce effects on normal tissue and confine their effects to diseased tissue.

CURRENT APPROACHES & CHALLENGES

Treating cancer with chemotherapy or radiation is flawed for reasons similar to surgery. These approaches are akin to ancient treatments for infectious agents like syphilis or malaria, in which the patient was treated with a poison-like arsenic that hopefully killed the infectious agent faster than the host. A miraculous cure could be achieved on perhaps one patient out of a hundred, a few were poisoned to death, and the majority got very sick from the treatment and weren't helped. Advances in care standards allow very potent chemotherapy or radiation regimens to be used today, but the fundamental paradigm remains largely unchanged.

To significantly improve chemotherapy, the effects of the treatment must be confined to the cancerous tissue while sparing normal tissue. Attempts to confine the toxic effects to cancer cells have included a number of unwieldy techniques, such as coupling toxic agents with monoclonal antibodies and using various encapsulation techniques. Products based on these technologies have been difficult to manufacture, offer limited specificity for certain tumor markers, and are therefore effective only on a limited subset of tumors. Further, these products can produce side effects that can be life threatening. Because the immune system works by maintaining a detailed "picture" of what "normal" looks like, it goes after almost any large, exotic molecule. An immunologic response is triggered by an


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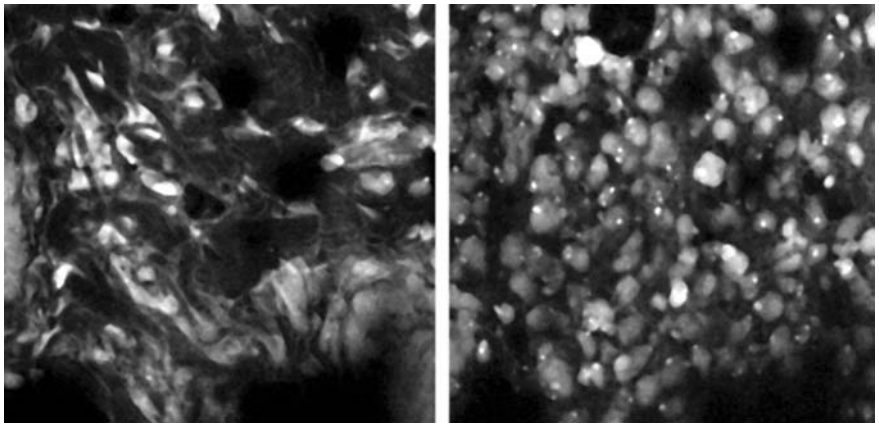
REVISITING INTRALESIONAL DELIVERY OF CANCER TREATMENT

I was recently invited into an operating room to observe radiofrequency ablation on a patient with multiple tumors in one lobe of his liver. The patient wasn't considered a candidate for resection of the liver on multiple grounds. The number of tumors would require removal of too much liver tissue, risking adversely compromised liver function. Also, a large tumor was situated very closely to the portal and vena cava veins. I watched a surgical team of two surgeons, multiple nurses, a radiologist (to read the ultrasound and MRI images and actually place the probe into the tumor), and a company representative monitoring performance of the RF device. As the probe was being inserted into the tumor, I heard one of the surgeons comment on the closeness of the tumor to the vena cava. He asked, "What will happen if we get too close and burn the vena cava." The response from the chief surgeon was "you better hope there is a vascular surgeon on this floor because we won't be able to close the wound." The radiologist and assistant at that point decided to stop inserting the probe any closer to the big vein. More telling was the assistant's comment on the effects of this decision. He said, "We don't have a chance of killing all the tumor, therefore with all this we are only buying him a little more time." A slight nod agreement from the chief surgeon was his only response.

FIGURE 1

Distribution of PV-10 is monitored in mouse tissue using multiphoton microscopy. Drug present in normal tissue (left) is located primarily in fluids surrounding cells whereas cancerous tissue (right) shows extensive uptake into cancer cells.



"altered-self" so alteration of a normal large molecule virtually guarantees a response. Coupling an antitumor agent to a monoclonal antibody of human origin can trigger an immunologic response almost immediately. This response at the very least will negate the effectiveness of treatment, but a severe anaphylactic response with life-threatening consequences is also a possibility. Additionally, the binding site of the antibody has to present a "foreign" configuration to the host (idiotype:anti-idiotype reaction). The anti-idiotype reaction may be an important "brake" in the immune systems response, which may further limit effectiveness.

The immune systems' exquisite sensitivity and specificity also works against antibody-derived antitumor therapies. Antibodies are directed against only one epitope in any antigen. Therefore, a slight alteration in a specific epitope in one patient may preclude effectiveness by a monoclonal-targeted therapy that works well in others. A more common problem occurs when the antigen target is confined to a limited subset of tumors. For example, anti-folate-receptor antibodies have little or no use in prostate cancer because folate-receptor levels generally aren't elevated in these tumors. Another example is use of anti-estrogen-receptor monoclonal antibodies to treat breast cancer. This approach is a far cry from "a cure for cancer" as touted in the popular press by a cancer researcher in a prominent government cancer facility. In reality, as little as 20% of breast cancer patients may be candidates for anti-estrogen-receptor antibody treatment. Of those patients, only a fraction may actually respond to treatment even though they have estrogen-receptor-positive tumors. It may be that the very large antibodies (160,000 Daltons) don't penetrate tissue to get to the needed sites. It is also possible that the receptor- positive cells modulate off the receptor or that in some patients there is a subtle alteration in the estrogen receptor epitope targeted by the antibody so that it can't bind its target. It may also be that the host's immune system recognizes the anti-estrogen-receptor antibody as foreign and neutralizes it. Therefore, large molecule targeting of chemotherapy agents is likely to remain limited in effectiveness and tremendously expensive.

To improve the effectiveness and safety of chemotherapy, one can design a tumor-specific agent. Lesion-specific delivery of therapy can also be used. Combining both would further potentate the effectiveness of the treatment. A number of attempts to use

REVISITING INTRALESIONAL DELIVERY OF CANCER TREATMENT

Table 1. Treatment of Human Breast Tumors (Lab Animal Model)

Human Tumor Cell Line*	Mice Cured
MCF-7 (ER+)	4/4
MCF-7 (ER-)	4/4
T-47D	4/4
HTB-133	4/4

** Similar results have been obtained with other tumor lines, including renal carcinoma, multiple-drug-resistant lung carcinoma, hepatocellular carcinoma, and prostate carcinoma. Spontaneous tumors treated in animal patients include: cutaneous melanoma, equine sarcoid, canine fibrous sarcoma, canine bladder tumor, and feline squamous epithelial carcinoma.*

these methods have been developed. Lesion-specific therapy of liver tumors is one prominent example. In the US, radiofrequency (RF) or cryoablation of primary or metastatic tumors to the liver is available. Outside the US, percutaneous injection of absolute ethanol into liver tumors under ultrasound guidance is common. However, these techniques still fail to confine their effects soley to diseased tissue because they are equally effective in ablating normal tissue. This limits effectiveness and risks severe or life-threatening side effects. Ablative techniques, such as RF and cryoablation, while a step in the right direction, remain hampered in their effectiveness and safety similar to other less-focused techniques. For example, if a liver tumor is non-resectable due to its location near major blood vessels, RF and cryoablation may be equally ineffective in treating the tumor for fear of damaging critical vasculature.

Another technique that has been attempted to limit toxicity of chemotherapy agents while increasing effectiveness is confining the area treated by limiting diffusion of a highly toxic and concentrated agent. Examples of these techniques include isolated perfusion for the treatment of metastatic melanoma and for non-resectable liver tumors. Basically, one tries to clamp or tie off blood supply to the treatment site for a limited time and deliver a high dose of agent. Eventually, the highly toxic agent will gain access to tissue outside the area being perfused, and because the agent isn't specific for diseased tissue, severe systemic side effects can occur.

Direct intralesional delivery of currently available antitumor agents like 5-FU have met with so little success that this approach hasn't gained acceptance. The effects of this type of agent have little more effectiveness than direct delivery of battery acid. In one study, 5-FU was delivered intratumorally into cutaneous melanomas. Only a couple of tumors out of a couple of dozen treated responded. The addition of epinephrine increased the effectiveness to about 4 out of 14 tumors treated. As in the case of isolated perfusion, the use of intralesional delivery of highly toxic and non-specific agents still eventually exposes the entire body to the effects of the drug that can lead to severe systemic side effects.

TUMOR-SPECIFIC SOLUTION

To gain maximum effectiveness and safety, tumors must be treated with an agent that only affects diseased tissue. Intralesional delivery of tumor-specific agent can further potentate the efficacy and provide an additional margin of safety. Provectus Pharmaceuticals, Inc. has developed a suite of compounds whose effects are almost completely confined to diseased tissue. Even though the company's initial preclinical studies have shown that the agents can be effective by delivery we have, it has chosen to maximize the chance of success by using the agents initially via intralesional delivery. Further, because the mechanism of targeting to only diseased tissue is known, Provectus can rapidly screen pre-existing compounds with known human safety profiles and determine which ones will specifically target only diseased tissue. Even though the company has a suite of "new drugs" that only target diseased tissue, to get a product to market rapidly, it has chosen to advance a pre-existing compound (PV-10) for a variety of applications, including intralesional treatment of cutaneous melanoma, breast carcinoma, and liver tumors. Choice of these applications was determined by sorting through a number of medical and technical reasons, market forces, and regulatory issues.

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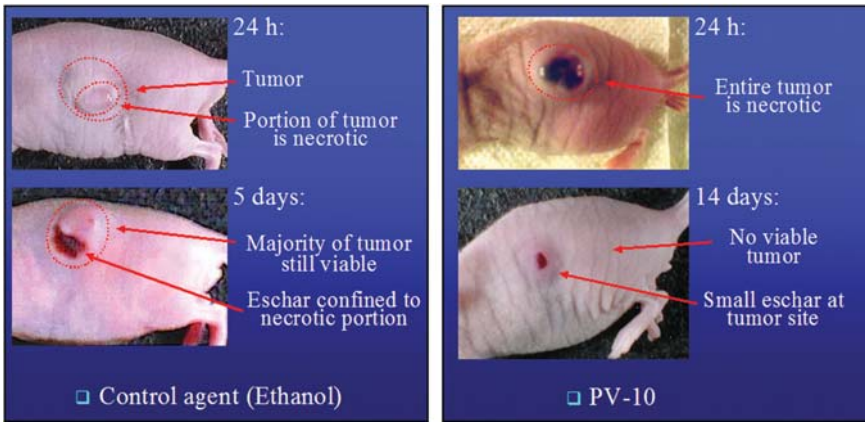
As a director of a small pharmaceutical company that must interact daily with investors, I am continually amazed by the number of investors that are attracted to a particular company solely because they or someone close has a disease that the company is developing a product for. Even though Provectus Pharmaceuticals' new antitumor agent has very broad spectrum applicability to a wide variety of tumors, one particular fund manager kept asking me questions only about treatment of liver tumors. This went on throughout a several-hour discussion. Finally, near the end of the meeting, the fund manager revealed that he was a liver cancer survivor and had been treated by organ perfusion therapy about 3 years before. He said, "Even though they tried to keep the drug in my liver, I was so sick I wanted to die." He continued, "I have 2 more years to go to feel safe, and if it comes back, I never want to be treated the same way again."

FIGURE 2

Chemoablation of a liver tumor in a mouse model using ethanol via intralesional delivery is ineffective in resolving the tumors and cures no mice (0/5). More damage is done to surrounding normal tissue than to diseased tissue. In contrast, the effects of PV-10 are confined to tumor tissue. Small wounds seen in PV-10-treated mice resolve, and the treated area is difficult to discern later. All mice are routinely cured (5/5).



MECHANISM OF TUMOR SPECIFICITY

PV-10 (Rose Bengal) when in the right solvent and conditions will confine its antitumor effects almost exclusively to cancer tissue. PV-10 has as a high solubility in water (approximately 10% w/v). However, when formulated as a solution with injectable saline as the diluent, PV-10 will partition out of the saline into a hydrophobic environment. And the intracellular conditions in tumor tissue are ideal for this. The intratumoral environment usually is acidic compared to surrounding normal tissue (eg, pH 6.4 to 6-7 compared to 7.2 to 7.4). Therefore, PV-10, when given systemically, will remain selectively localized in tumor tissue. When PV-10 is given intralesionally, it and its antitumor effects are confined to the tumor. Any drug that doesn't associate with tumor cells is cleared from the normal tissue. PV-10 is rapidly eliminated from normal tissue (30-minute half-life when injected intravenously, and 7-hour half-life as an intramuscular depot).

Further, PV-10 only partitions into the membranes of cancer and other diseased cells, thus confining its effects to these cells at the cellular level (Figure 1). The conditions that exist in the diseased cells that allow PV-10 to selectively enter them are not fully known. However, among other alterations, the membrane fluidity is higher, which is advantageous for partitioning of PV-10 into the membrane. Additionally, in many cancer cells, the receptor density of many receptors is elevated (eg, lipoprotein receptors). PV-10 may also take advantage of receptor-mediated processes like lipoprotein receptors to enter the cell. PV-10 would then be transported to the lysosomes along with complex hydrophobic molecules with which it is associated.

At the subcellular level, PV-10 exerts its effects by stimulating a natural process through which cells normally commit "suicide." Lysosomes that contain degrative enzymes are an important part of the cellular process that results in cell death. Release of lysosomal contents is an early step in the pathway. The composition of the lipids (highly fluid) in the lysosomal membrane is ideal for partitioning of PV-10 into the membrane. Further, the intralysosomal environment is very acid (pH 4.0), which makes the environment ideal for PV-10. Once associated with diseased cells, PV-10 disrupts the integrity of lysosomal membranes. The lysosomes rupture or leak, releasing their contents in a process that mimics the normal

REVISITING INTRALESIONAL DELIVERY OF CANCER TREATMENT

cascade of events that occurs when cells undergo apoptosis. Therefore, cell death is not like that produced by a toxic agent but more like the normal cell "suicide" process. Further, PV-10 doesn't enter the nucleus or work by damaging genetic material. PV-10 isn't carcinogenic, mutagenic, or likely to be teratogenic, especially when delivered by an intralesional route. Therefore, the possibility is remote for long-term sequalae of a second tumor in contrast to that of most current anticancer therapies.

PERFORMANCE *IN VIVO*

As shown in Table 1, a small volume of PV-10 delivered intralesionally results in resolution of all breast tumors in a laboratory animal model. Figure 1 shows that there is no apparent damage to surrounding tissue. This has been confirmed by histopathologic examination of the effects on these tumors. As shown in Figure 2, the tumors rapidly resolve, and the treated animals have been held up to a year with no return of tumors at the primary or a remote site. For most tumor models, one treatment results in cure of the animals. However, on a rare occasion due to a defect in the technique of drug delivery, a tumor may not be fully resolved. Because there are virtually no side effects, the tumor can be retreated. This is in stark contrast to the use of many toxic chemotherapy agents in which therapy has to be halted due to systemic side effects, often focused on the immune system, and resulting in severe immunosuppression.

Currently PV-10 is being tested in a Phase I clinical trial of Stage III melanoma patients treated by intralesional delivery. The Phase I trial is primarily a dose-escalation study for safety. However, because the systemic safety profile is known for this agent, the initial doses are at anticipated efficacy levels, allowing us to assess both safety and initial effectiveness in Phase I. A similar Phase I clinical trial on breast cancer patients is being performed at efficacy levels. To date, early results from these trials are similar to the results observed in tumors in experimental animals and with spontaneous tumors in animals. No severe local or systemic adverse events have been reported, and complete ablation of tumors has been observed.

In conclusion, where previous attempts at using highly toxic chemotherapy agents have had little success and the effects were not too dissimilar from using a highly concentrated acid, the key to success using intralesional delivery is to combine the method with an agent like PV-10 whose effects are confined to diseased cells. Laboratory studies using tumor models and treatment of spontaneous tumors have validated this approach, while early response in human clinical trials is similar to that of the preclinical animal studies. Clinical trials are continuing in melanoma and breast carcinoma, and are expected to begin soon for liver cancer.

BIOGRAPHY

Dr. Craig Dees is the Chief Executive Officer of Provectus Pharmaceuticals, Inc. He has spent more than 20 years in Senior Management positions at Photogen Technologies, Inc.; the Oak Ridge National Laboratory; LipoGen, Inc.; and TechAmerica, Inc. Dr. Dees was a Founder, Senior Scientist and Founding Director of Photogen before Provectus was formed. His responsibilities have included product design and development in the fields of ethical vaccines, cosmetics, human diagnostics, and over-the-counter pharmaceuticals. His development record includes the first live viral vaccine produced by recombinant DNA technologies and the first recombinant antigen human diagnostic assay. Dr. Dees has also successfully licensed a number of proprietary cosmetic products. In addition to design and development activities, he has been responsible for business and market applications, regulatory affairs, and commercialization of human and veterinary medical products. Awards include an R&D 100 for an industrial enzyme, an Inventor's Forum New Product Award for a skincare product, and a First Sarber Award for outstanding research in virology. Dr. Dees earned his PhD in Molecular Virology from the University of Wisconsin, Madison, his MS in Immunology from Auburn University, and his BS in Microbiology from Brigham Young University.

ABSORPTION ENHANCEMENT

Promoting the Oral Absorption of Drugs in Humans Using Gastro-Intestinal Permeation Enhancement Technology (GIPET)

By: Thomas W. Leonard, PhD; Edel O'Toole, Fiona Brennan, PhD; and David J. Brayden, PhD

ABSTRACT

Overcoming the poor oral absorption of high-value therapeutics, including peptides, is one of the most important and challenging goals in drug delivery. Gastro-Intestinal Permeation Enhancement Technology (GIPET, Merrion Pharmaceuticals Inc., Wilmington, NC.) attempts to address this issue by safely delivering drugs across the small intestine in therapeutically relevant concentrations. GIPET is based primarily on promoting drug absorption through the use of medium-chain fatty acids, salts, and derivatives (GIPET I), formulated in enteric-coated tablets. GIPET II comprises mixtures of mono- and di-glyceride fatty acids in a solid dose format (Box 1). Importantly, these excipients are generally regarded as safe (GRAS) and do not result in a change in chemical composition of the active ingredient. To date, 300 volunteers have been administered GIPET formulations in 16 Phase I studies of 6 separate drugs comprising both single- and repeat-dosing regimes. Oral bioavailability of alendronate, desmopressin, and low molecular weight heparin in humans was increased using GIPET formulations compared to unformulated controls. GIPET was well tolerated by human subjects. Using fluxes of markers of epithelial permeability, effects of GIPET on the human intestine were shown to be rapid, short-lived, and reversible *in vivo*. The combined data suggests that GIPET formulations have a real potential as a platform technology for safe and effective oral drug delivery of poorly absorbable drugs.

INTRODUCTION

In 1995, Amidon and colleagues recommended the biopharmaceutical classification system (BCS) for describing gastrointestinal absorption behavior of drugs.[1] The BCS groups drugs into one of four classes based on solubility and permeability characteristics (Table 1). Technologies to enhance oral absorption of poorly absorbed compounds can be divided into two general categories, those involving chemical modification to the compound, and those that depend on physical interactions. Those techniques dependent on physical interactions are generally preferred by the pharmaceutical industry because they offer a more direct path toward regulatory approval for compounds that are already approved or are in advanced stages of development. Physical techniques can be directed toward increasing dissolution/solubility in the intestinal milieu, or increasing intestinal wall permeability. Delivery of drugs that are insoluble but are permeable (Class II in the BCS categorization) can generally be improved with solubilizing approaches, whereas soluble but poorly-permeable drugs (Class III), including most peptides, are amenable to approaches that improve the ability of the compound to cross the gut/epithelial interphase.[2,3] This may be achieved by direct action on the gut epithelium, or by forming mixed micelles or other sorts of physical interactions between the drug and the enhancer that enhance permeability, or both of these.

There have been many attempts to promote oral absorption of poorly absorbed drugs throughout the past 15 years, but the majority have not been commercially successful. Reasons for these failures include the inability to deliver therapeutic levels of drug over a sustained period of time and safety issues associated with new chemical compounds used as enhancers. Also associated with these attempts is the high cost of goods (due to the poor efficacy of the enhancer system), which results in the need for

THE ADVANTAGES

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Liquids naturally offer faster and increased absorption and availability of active ingredients.

Increased Profit Potential
Add up all the advantages. Expect higher sales…and high margins!

Deliver Incompatible Compounds Deliver incompatible compounds in a single dosage form with different release profiles.

Multiple Release Profiles
Incorporate one or more release profiles into a single dosage form such as immediate, enteric, targeted, chronotherapy and pulsatile.

Smaller Capsules
Hard-shell capsules have thinner wall construction, allowing them to contain more ingredient in a smaller capsule versus thicker-shelled soft gel capsules. Hard shells have faster and more complete dissolution than soft gels.

Less Odor and Less Irritation
Reduces unpleasant ingredient taste and odor commonly found with tablets and traditional capsules. And, liquids provide less irritation than traditional delivery methods.

Tamper Proof Sealing
Band sealing reduces tampering and provides a non-permeable barrier to retard oxidation and increase shelf-life.

Unique Appearance
This new delivery system stands apart from look-alike products that crowd retail shelves.

Faster Development
Multi-phase, multi-compartment capsules reduce the development time compared to bi-layer tablets to get a new product into clinical trials faster.

Compounds
Deliver Pharmaceutical, bio-pharmaceutical and nutraceuticals in a single dosage form.

Multi-Phase System
Compounds can be delivered with the most advantageous pharmacokinetic profile such as liquids and solids

InnerCap™ Technologies, Inc

Patent Pending US-2005-0008690-A1

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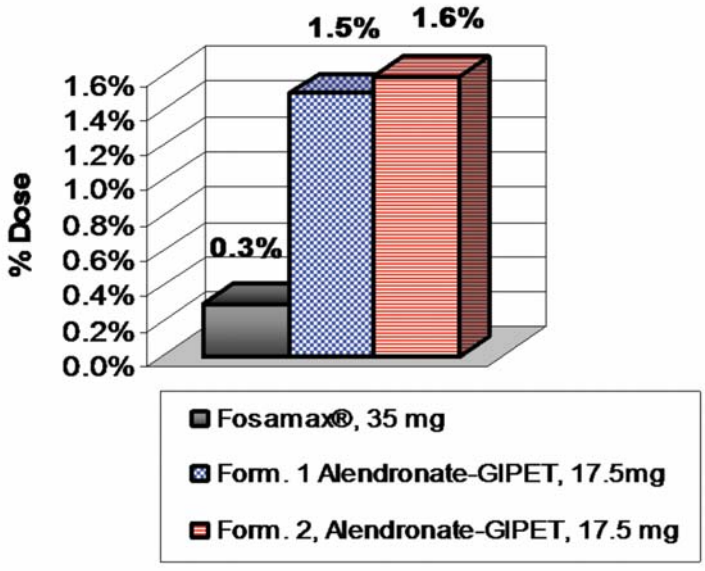
FIGURE 1

Mean urinary excretion of alendronate expressed as % administered dose from a single dose of GIPET solid dose formulations in humans. Reference: Fosamax®, 35 mg; Alendronate, Test: 17.5 mg with low (Form 2) or high concentrations of GIPET I (Form 1). N = 16. Coefficients of variation were: Reference Fosamax® - 33.6%, Form 1 - 40.5%, and Form 2 - 106.8%.



Box 1. Composition of GIPET Solid Dose Oral Delivery Technologies

GIPET I Technology

- Medium-chain fatty acids and salts thereof
- Solid dosage forms (enteric-coated tablets)

GIPET II Technology

- Mono-/di-glyceride fatty acids
- Solid dosage forms (enteric-coated soft gel/hard capsule shell)

GIPET III Technology

- Novel branched, cyclic, and straight chain fatty acids
- Solid dosage forms (enteric-coated tablets and/or capsules)

significant amounts of active pharmaceutical ingredient (API). Lack of reliable and predictive *in vivo* animal models and the inability to convert technology into practical and reproducible solid dosage forms have also been an impediment to reaching commercial success.

GIPET is a platform technology demonstrated to enhance bioavailability of a variety of compounds, most of which belong to the BCS Class III. These compounds include most peptide, polysaccharide, and oligonucleotide molecules that traditionally have been administered parenterally at significant cost and inconvenience to patients. This review provides an evaluation of the technology with a particular emphasis on data that have been achieved in Phase I human trials.

GIPET TECHNOLOGY

In 1991, it was shown that paracellular absorption of polar marker molecules across isolated rat colonic mucosae was increased by medium-chain fatty acids at selected concentrations *in vitro*.[4] Anderberg et al demonstrated that part of the mechanism of action of GIPET I in the *in vitro* human intestinal cell line, CACO-2, was used to promote absorption across intestinal epithelial tight junctions at a concentration of 13 to 16 mM, thereby effecting cytoskeletal changes favoring permeation of small polar molecules.[5]

While it is relatively simple to show enhanced permeation using isolated tissue mucosae or perfused rodent intestinal segments using solutions of excipients with the active, it is another set of challenges to advance a preclinical concept to a marketable formulation that can be used in human patients. The development of GIPET technologies was facilitated by the need for solid dosage form presentations for oral enhancement techniques. The general format of GIPET dosage forms is enteric-coated tablets or capsules comprising the enhancer system and the drug in an appropriate matrix. Importantly, for GIPET I and II systems, the excipients used as

FIGURE 2

Plasma profile of anti-Factor Xa activity from the oral delivery of LMWH-GIPET I in humans. ■ 90,000 IU LMWH/ high dose GIPET; ◆ 45,000 IU LMWH/ low dose GIPET; ▲ SC reference, 3,200 IU LMWH. N = 14 to 16 subjects.

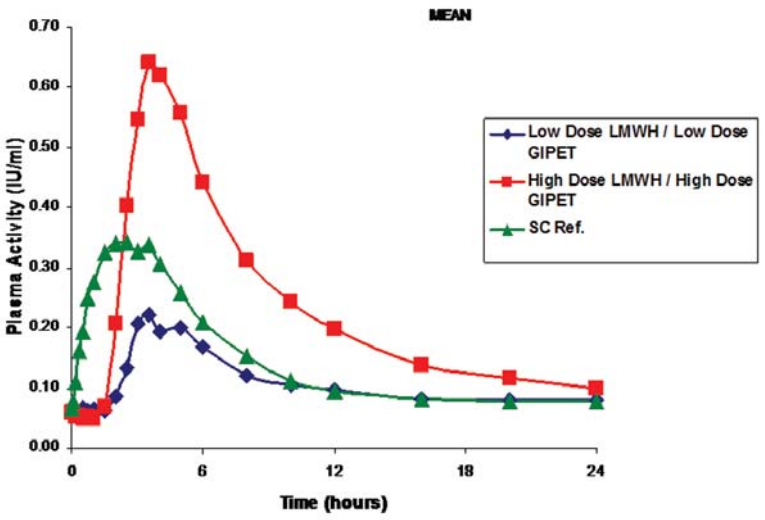


Table 1. The Biopharmaceutical Classification System (Amidon et al, 1995)

Class II Low solubility High permeability	**Class I** High solubility High permeability
Class IV Low solubility Low permeability	**Class III** High solubility Low permeability

enhancers were specifically selected due to their GRAS status. Not only do medium-chain fatty acids enjoy GRAS status, they are also common food components; they are present in milk at a level comprising more than 1.2% of the total fatty acids.[6] GIPET I and II systems have been tested orally in rats, dogs, and humans to establish safety profiles and efficacy. The absorption promoter and the drug should be released at the same rate and at appropriate concentrations close to the absorbing epithelium to maximize efficiency of the drug/enhancer/epithelium interaction.

PHASE I TRIALS OF GIPET

GIPET has been tested in a range of doses with six poorly-absorbed drugs in a total of 16 Phase I studies. Table 2 shows the human oral bioavailability data for the six drugs in humans. Overall, a 5- to 14-fold improvement in oral bioavailability was seen compared to controls. Detailed pharmacokinetics from human trials are described further for three specific examples, all of which are soluble and poorly permeable compounds: a bisphosphonate, alendronate; a polysaccharide, low molecular weight heparin (LMWH); and a peptide, desmopressin.

Alendronate sodium (Fosamax®, Merck) is approved as both once-a-day and once-a-week tablets for the treatment and prevention of post-menopausal osteoporosis in women and also for men requiring an increase in bone mass density. Oral bisphosphonates are very poorly absorbed; approximately 0.65% of an oral dose of alendronate is absorbed.[7] Bisphosphonates are currently not administered as enteric products as this administration route results in even less absorption. All current oral formulations of bisphosphonates are associated with dysphagia and esophageal reflux. The tablets must be taken in the morning with a full glass of water on an empty stomach to ensure some drug is absorbed, and patients are required to remain upright for at least 30 minutes following administration to minimize esophageal erosion from the gastric irritation. This complex dosing regime severely decreases compliance.[8] Injectable bisphosphonates, pamidronate (Aredia®, Novartis) and zoledronic acid (Zometa®, Novartis) are used as chemotherapeutic agents for metastatic bone cancer.[9] Efficacy in this indication requires a greater bioavailability than can currently be delivered orally. The intravenous dosage forms also result in some discomfort, albeit on a monthly basis, and requires patients to spend several hours in outpatient clinics at considerable expense. An oral formulation of bisphosphonates with significantly higher bioavailability would certainly benefit this subgroup of patients.

A GIPET I-enhanced alendronate tablet containing 17.5 mg of alendronate was administered orally to 16 healthy subjects. Bioavailability was compared with that achieved after administration of 35-mg Fosamax® tablets. Urinary excretion data indicated that GIPET conferred a 5-fold increase in the oral bioavailability of alendronate formulations over the reference compound (Figure 1). This achievement is noteworthy from two perspectives. First, it is a very significant improvement in bioavailability over the current formulation. Such improvements in bioavailability should allow expansion of indications for bisphosphonate tablets into those areas that are now treated by injections. Second, these results are achieved

FIGURE 3

Plasma profile of the oral delivery of desmopressin-GIPET II in humans. ■ Desmopressin-GIPET (200 µg, PO capsule); □ Desmopressin, Minrin®, (200 µg, PO tablet); ▲ Desmopressin (4 µg, SC reference). N = 18 subjects.

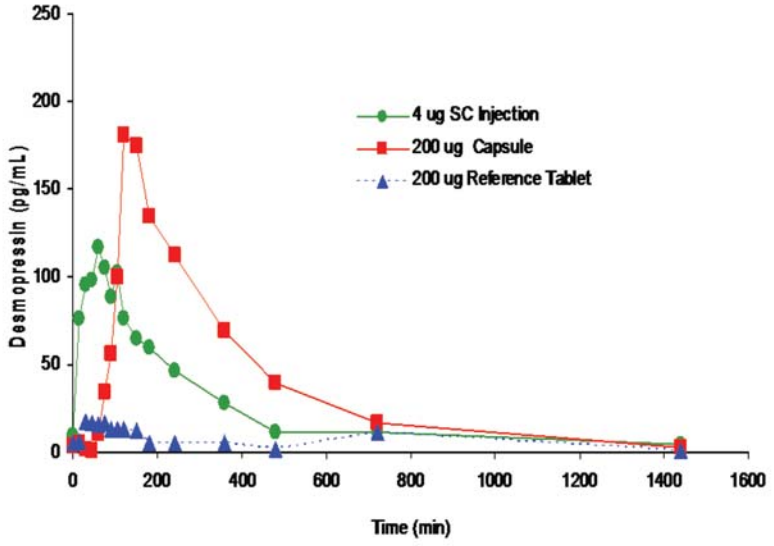


Table 2. Phase I Oral Bioavailability Data With GIPET

Drug (MW)	GIPET	Reference	Oral Bioavailability (%)**	Fold Increase Over Control ***
Alendronate (323)	I	Fosamax® (oral)	8.4	5
Desmopressin (1,069)	II	S.C.	2.4	13
LMWH* I (approx 4,500)	I	S.C.	9.0	-
LMWH* II (approx 6,000)	I	S.C.	8.0	-
Antisense I (6,350)	I	I.V.	4.9	-
Antisense II (7,284)	I	I.V.	6.9	-

** LMWH: Low Molecular Weight Heparin*

*** % Oral Bioavailability refers to the bioavailability of these compounds using GIPET relative to the parenteral dosage form.*

**** Fold Increase Over Control is the improvement in oral bioavailability resulting from the GIPET formulation relative to an unenhanced oral control.*

by enteric-coated tablets, which eliminate gastric administration and the associated gastric and esophageal issues.

Low molecular weight heparin (LMWH) is used as a prophylactic anticoagulant treatment to prevent deep vein thrombosis or pulmonary embolism following hip or knee replacement surgery, and must be given by subcutaneous injection due to its low bioavailability.[10] As this is an acute therapy, treatment usually ends when a patient leaves the hospital. Oral warfarin, which has a very narrow safety profile, is often used if therapy is to be continued at home. An oral formulation of LMWH would reduce healthcare costs as it could be easily administered on an outpatient basis, eliminating the need for the intensive therapeutic monitoring that is carried out on new warfarin patients due to its toxicity. LMWH-GIPET I was formulated in coated tablets containing 45,000 or 90,000 IU of a LMWH (average molecular weight of about 4,500) with GIPET I. Oral bioavailability was compared to the standard subcutaneous dose of 3,200 IU following administration to 14 to 16 healthy human subjects. Mean data for the anti-FactorXa assay over time is shown in Figure 2, and the overall data is summarized in Table 3. Oral bioavailability of 3.9% to 7.6% with respect to the subcutaneous route was achieved. With the 90,000-IU tablet, therapeutic levels of anti-FactorXa activity were seen in all subjects, and the responses were sustained in most subjects over a time course comparable to the subcutaneous delivery. Oral bioavailability of 8% in humans has also been achieved using GIPET II with another LMWH (average molecular weight of about 6,000) while up to 18% oral bioavailability was seen with LMWH in dogs with GIPET III (data not shown).

Desmopressin, a synthetic peptide analogue of arginine vasopressin, is used as an antidiuretic agent for treatment of vasopressin-sensitive *diabetes insipidus*, polyuria, and polydypsia.[11] Oral bioavailability is low, ranging from below the limit of detection of the assay to 5%. There is considerable intrasubject variation. With a direct relationship between the amount absorbed and the pharmacodynamic response, an improved oral formulation could lead to better efficacy

Table 3. Phase I Oral Bioavailability Data: LMWH-GIPET 1

PK (Pharmacokinetic Parameters)	45,000 IU LMWH GIPET 1	90,000 IU LMWH GIPET 1	3,200 IU SC Ref.
Oral bioavailability (%)	3.9 ± 3.5	7.6 ± 4.8	N/A
Coefficient of variation (%)	89.1	62.9	N/A
Number of responders with levels > 0.1 IU/mL (%)	60 (9/15)	100 (14/14)	100 (16/16)
Number of responders with levels > 0.1 IU/mL for > 6 hours (%)	13 (2/15)	71 (10/14)	81 (13/16)
Total duration > 0.1 IU/mL (Hours)	2.6 ± 3.6	10.6 ± 5.4	7.1 ± 1.3

associated with a high level of compliance. When desmopressin was formulated in a GIPET solid dose format and administered orally to 18 human subjects, 2.4% bioavailability relative to the subcutaneous route was measured. Notably, this value was a 10-fold improvement over the 0.2% value seen in this study in subjects who were administered with the currently marketed Minirin® tablet (Ferring Pharmaceuticals) (Table 4, Figure 3). More importantly, the CV around the AUCs dropped from more than 240% to less than 90%. The AUC CVs for the GIPET dosage are similar to those for the injectable product.

SAFETY STUDIES OF GIPET IN PRECLINICAL MODELS

The absorption-promoting excipients of the GIPET technology are approved food additives in both the US and Europe. The available data demonstrate the low toxicity of fatty acids and their salts, which is consistent with their long history of use as food additives. GIPET components enjoy favorable regulatory status. Several regulatory bodies have reviewed the data on safety and concluded that the fatty acids and their salts used in the GIPET formulations are low in toxicity.[12]

For example, the fatty acids used in GIPET are considered GRAS by the US FDA. When reviewed by the FAO/WHO Joint Expert Committee on Food Additives, component fatty acids in GIPET were not limited to a specific allowable daily intake because it was judged that the presence of these materials in food would have no impact on human health.[13] Finally, the EU Scientific Committee for Food has reviewed the safety data for these excipients and determined them to be safe in use.[14]

Multiple safety studies of GIPET enhancers have been carried out in rats and dogs with the objective of evaluating the potential for adverse effects on the gastrointestinal tract. In these studies, doses of up to 1 g per day were given for as long as 4 weeks without effect on clinical signs or clinical laboratory parameters, and failed to produce any gross or microscopic pathology in the gastrointestinal tract.

SAFETY STUDIES OF GIPET IN CLINICAL STUDIES

The Phase I studies on the six drugs that have been carried out comprised 800 exposures to GIPET in 300 volunteers. In some studies, individuals were safely dosed up to six times with GIPET formulations in order to show that exposures could be safely given on a repeated basis. A legitimate concern with the use of intestinal absorption-promoting technologies is that the epithelium may not have time to recover before the next dose. Although the clinical experience thus far has not suggested that this is an issue *in vivo*, intestinal permeability studies were carried out in human subjects following intrajejunal (IJ) administration of GIPET I followed by sugar molecules whose oral absorption is typically low and largely restricted to the tight junction route. The aim was to establish intestinal permeability recovery time in the presence of a typical fatty acid component of a GIPET formulation. The polar sugar, mannitol (MW 182), is absorbed paracellularly across the gut and is excreted unchanged in the urine. Oral bioavailability of mannitol is approximately 25%, and this amount is retrieved in the urine because it is freely filtered and not reabsorbed by renal tubules. Another polar disaccharide sugar, lactulose (MW 342), is also absorbed paracellularly, but only to a level of 1% due to its larger molecular radius. The ratio of the two agents in urine is a well-established, non-invasive indicator of human intestinal permeability *in vivo*.[15]

When the tight junctions are open or if the epithelium forms a less-restrictive barrier, the urinary lactulose:mannitol excretion ratio (LMER) should increase because lactulose absorption should be preferentially increased. In an open label partially randomized study using up to 24 human subjects, the marker molecules, mannitol (2 g) and lactulose (5 g) were given orally at time 20, 40, or 60 minutes following intrajejunal instillation of GIPET I. The combined data showed that only when the sugars were administered 20 minutes after the fatty acid, the urinary LMER ratio increased (Table 5). Thus, in subjects receiving three

Table 4. Phase I Oral Bioavailability Data: Desmopressin-GIPET II

Treatment	AUC Last (±CV%)	Relative Bioavailability (±CV%)
Desmopressin-GIPET II (200 µg, PO capsule)	840 ± 729	2.4 ± 2.9
Desmopressin (Minrin®) (200 µg, PO tablet)	159 ± 383	0.2 ± 0.2
Desmopressin (4 µg, SC reference)	539 ± 517	N/A

AUC Last: Area under the curve; CV%: coefficient of variation; N = 18 in each group

Table 5. Timing of Effect of GIPET I on Human Intestinal Permeability Using Urinary Excretion of Polar Sugars as a Surrogate Marker

Group	LMER (CV)	N	Statistics
A. Sugars	0.02 ± 0.01 (66.3)	24	-
B. GIPET I 20 mins before sugars	0.03 ± 0.01 (70.4) *	22	P < 0.01
C. GIPET I 40 mins before sugars	0.02 ± 0.01 (38.9)	22	NS
D. GIPET I 60 mins before sugars	0.02 ± 0.01 (31.9)	23	NS
E. Sugars	0.02 ± 0.00 (29.5)	22	NS

LMER: lactulose:mannitol urinary excretion ratio; CV = coefficient of variation. Treatments were 0.5g GIPET I in 15-mL solution administered via perfusion tube to the jejunum in the presence and absence of 2 g mannitol / 5g lactulose / 9 g glycerol administered as 100-mL solution orally at different time intervals. Statistical significance was assessed by paired t-test against group A. Group B was statistically different from baseline if two high responding outliers were removed from the analysis. Data supplied by Dr. SJ Warrington, Hammersmith Medicines Research, Hammersmith Hospital, London, UK.

separate doses of GIPET I, the effect of the agent on intestinal permeability was temporary and increases in permeability were reversed at 40 and 60 minutes. Importantly, the three IJ doses of GIPET I were considered safe and well tolerated in the human subjects. Furthermore, studies testing the effects of GIPET I on increasing intestinal [^{14}C]-poly (ethylene) glycol absorption in dogs were similarly suggestive of only a temporary effect of this major component of GIPET (data not shown). The combined data is not surprising because 17 billion enterocytes are normally replaced every day, and the entire epithelium of the small intestine is replaced every 5 days in humans.[16]

CONCLUSION

GIPET is a mature research-stage technology that has shown significant efficacy in human oral delivery studies of drugs that normally must be injected. The data show that a range of drugs of different structures can be delivered to therapeutic levels using two different solid-dose GIPET formulations. These include peptides, bisphosphonates, glucosaminglycans, and antisense oligonucleotides. The wide variety of poorly absorbed drug types that have now shown efficacy in Phase I trials using the GIPET oral delivery formulations suggests that the delivery system is a true platform technology that can be adapted for a range of biotech cargoes. Importantly, Phase I trials using 300 subjects revealed no toxicity of concern and, in addition, this finding was manifested in subjects receiving multiple doses of GIPET. Additional human studies revealed that the absorption-promoting effects of GIPET were transient and complete in less than 1 hour. The combined data provides additional arguments that suggest that the absorption promoter and the active ingredient need to be formulated as an enteric-coated solid dosage form in which the ingredients are gradually co-released as the formulation moves along the epithelium of the upper small intestine. Therefore, in contrast with GIPET technology, simple ad-mixing of solutions of promoters and active agents is unlikely to be effective *in vivo* because co-localized release cannot be guaranteed.

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BIOGRAPHIES

Dr. Thomas W. Leonard, Vice President and CSO at Merrion Pharmaceuticals, Inc., has over 23 years experience in pharmaceutical R&D, drug development, formulation, and manufacturing. He is a graduate of the University of South Carolina School of Pharmacy and earned his PhD in Pharmaceutics from Virginia Commonwealth University. He has written numerous publications and abstracts, and is the inventor of 25 issued and in-process patents in drug delivery and female healthcare.

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PRESSURE-SENSITIVE ADHESIVES

Silicone Pressure-Sensitive Adhesives Versus Tacky Gels

By: Stephen Bruner and John Freedman

INTRODUCTION

By definition, transdermal, drug delivery applications mandate the use of adequate adhesive systems, not only to keep the pharmaceutical agent in contact with the intended surface, but to facilitate sustained, controlled delivery. Engineers who determine the optimal silicone chemistry for their devices have a few options. While pressure-sensitive silicone adhesives (PSAs) have typically been considered optimal for transdermal applications, silicone gel technology has emerged as an excellent option.

To make an educated decision regarding chemistry choices, it's vital to understand the differences between silicone PSAs and gels in both composition and physical performance. After reviewing supplied forms and basic chemistry, NuSil Technology, LLC, compared these factors, as well as peel and tack data, to illustrate the strengths, advantages, and disadvantages of each technology.

HISTORIC PERSPECTIVE

Since 1979, PSAs have been a mainstay in transdermal, drug delivery. PSAs provide pharmaceutical companies the means to supply a range of active agents in a non-invasive, controlled-release system, as well as reduce the healthcare industry's dependence on gastrointestinal and needle-based administrations. The overriding benefits of these systems include improved patient compliance and steady drug levels within the bloodstream.

Estradiol, testosterone, and nitroglycerin are just a few of the compounds currently found in prescribed, transdermal, drug delivery systems. Over-the-counter (OTC) products, such as Dr. Scholl's Clear Away Wart Remover®, Neutrogena's On-the-Spot Acne Treatment®, and several brands of the nicotine patch, are examples of how this technology has moved readily into direct consumer applications. Estimates for growth in this area are 12% annually.[1] Some of the usual adhesives incorporated in transdermal, drug delivery systems are polyisobutylenes (PIBs), silicones, and acrylic-based PSAs. For this article, silicone-based PSAs are used for comparative purposes.

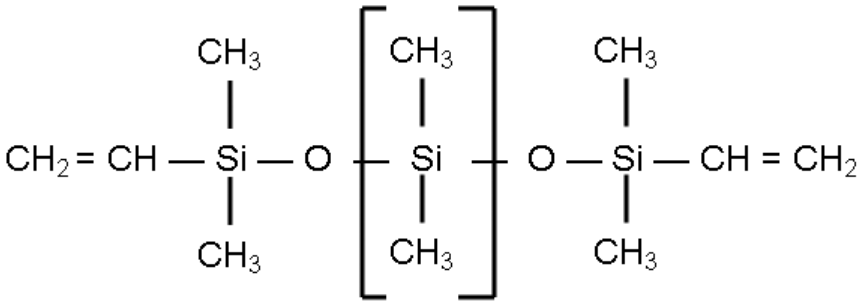
Silicones are good candidates for transdermal, drug delivery systems because they offer two major benefits to drug-device developers. First, silicones have a 50-year-plus history in biomedical applications and, in that time, a considerable body of work has been assembled that characterizes silicones as biologically inert.[2] In addition, silicones are ubiquitous in the medical device industry in both long-term, implantable devices, and external devices. Second is the compatibility/permeability of silicones with many pharmaceutical agents, not just hormones. Other compatible drugs include antidepressants; anxiolytics; vitamins B6, D, and E; antifungals; opioid and non-opioid analgesics; and antiviral compounds.[3]

SILOXANE CHEMISTRY

Silcones' compatibility and permeability with pharmaceutical agents is a function of the siloxane-based polymers and resins used to formulate

FIGURE 1

A Divinyl-Terminated, Dimethyl Polysiloxane's Hydrophobicity is Ideal for the Solubility of Pharmaceutical Agents



these systems, as well as the interaction potential created by the siloxane polymer backbone of repeating silicon and oxygen atoms. The two free pairs of electrons associated with each oxygen atom can form hydrogen bonds with proton donors, often resulting in different degrees of hydrogen bonding with reinforcing fillers. Despite its ability to form hydrogen bonds, silicone is considered hydrophobic in nature. The methyl constituency on the siloxane polymer backbone creates this effect. A vinyl-terminated, dimethyl polysiloxane can be seen in Figure 1.

This hydrophobicity is ideal for the solubility of pharmaceutical agents having mostly non-polar structures. Another characteristic of silicone systems is the large atomic volume of the silicon atom itself, which, along with the size and position of constituent groups, explains the virtually complete freedom of rotation around the Si-O-Si bond. Silicone polymers form helixes, and the bond angles of the silicon-oxygen bonds create large amounts of free volume in silicone elastomers. This free volume and the high compressibility found in silicones are associated with their permeability to certain gases and liquids. The gas permeability of silicone rubber is up to 100 times greater than natural or butyl rubber.

In the specific case of drugs or active pharmaceutical molecules, release rates in silicones are determined by the drug's solubility in a silicone and the diffusion coefficients of those drugs in silicones through the Higuchi equation[4,5] (Equation 1 corresponds to a matrix device, and Equation 2 corresponds to a reservoir device).

Equation 1.

$$Q = (D_{sil}\,(2A - C_{sil})\,C_{sil}\,t)^{1/2}$$

Where Q is the cumulative amount of drug released per device-unit area, A is the drug loading, C_{sil} is the drug solubility in the silicone, D_{sil} is the diffusivity of the drug in

Equation 2.

$$Q = ((D_{sil}\,C_{sil})/\,h_{sheath})*t$$

the elastomer, h_{sheath} is the thickness of the sheath in cm, and t is the time in days. Determination of these values is aided by additional research in this area that relates the molecular weight and melting point of the drugs to release rates, as well as demonstrates that the addition of fatty acid esters improve release rates of certain drugs.[4,6]

Silicone polymer chemistry can be modified to include different groups on the backbone. For example, trifluoropropyl methyl dimethyl siloxane copolymers are used in applications in which solvent resistance is required, while diphenyl silicone polymers are used in elastomeric formulations, when a high-refractive index is necessary (intraocular lenses or UV and heat protection). The diphenyl and trifluoropropylmethyl functionality may also affect drug solubility and, in turn, affect release rates. The concentration of these groups on the backbone can be easily altered and optimized for specific compounds. A divinyl-terminated, diphenyldimethylpolysiloxane copolymer structure is seen in Figure 2.

SILICONE PSAS

Silicone PSAs incorporate a high-molecular-weight polydimethylsiloxane polymer and a tackifying silicone resin dispersed in a solvent system. The solvent provides the system with viscosity control, as silicone components are virtually

Table 1. The tested materials, as well as their material, composition, and cure schedule.

Material Name	Material Composition	Cure Schedule
MED-1356	Dimethylpolysiloxane PSA, 35% Solids in Ethyl Acetate	37°C for 30 minutes, 150°C for 90 minutes
MED-1356 (peroxide- catalyzed)*	Dimethylpolysiloxane PSA, 35% Solids in Ethyl Acetate, 0.5 pph PD-50S Based on Solids	37°C for 30 minutes, 150°C for 90 minutes
MED-6340	Dimethylpolysilixane Gel, 100% solids	100°C for 30 minutes
GEL-9502-30	Diphenyldimethylpolysiloxane Gel, 100% solids	100°C for 30 minutes

** MED 1356 product is not supplied as a peroxide-cured product.*

impossible to process at room temperature with standard coating equipment. If containing a catalyst, silicone PSAs typically crosslink by curing after removing the solvent. Two systems are currently available: platinum-catalyzed and peroxide-catalyzed.

Platinum-catalyzed systems are common in PSAs and utilize vinyl-functional polymers, such as in Figures 1 & 2, and hydride-functional crosslinking polymers to cure in the presence of the catalyst. Curing of these PSAs is achieved through multi-zone ovens. The solvent is eliminated by a gradual increase in temperature from 60°C to 90°C.

Peroxide-cure systems employ benzoyl peroxide, or 2,4-dichlorobenzoyl peroxide, as a catalyst to drive a free-radical reaction and achieve cure. Curing is normally performed in a multi-zoned oven. Solvent removal is achieved through a gradual increase in temperature, starting at 60°C to 90°C to ensure that the peroxide catalyst does not cure while solvent is present. The temperature is then increased to 130°C to 200°C, although it is more commonly raised to 350°F maximum because of limitations of the coating substrate (ie, shrinkage and stretching), eliminating the peroxide through decomposition. A high-crosslink-density PSA can be better achieved through peroxide curing due to the ability to increase peroxide levels to 4%.

Converters of tape and adhesive-backed components take the liquid PSA and either wet coat in sheet form, for small applications, or in roll form (pilot coaters and full-width production coaters), when large quantities are required. The PSA may be applied on one or both sides of a substrate, such as Kapton®, Mylar®, Nomex®, foils, foams, and rubbers, or it can be coated directly onto a release film. Coat weights on supported film range in thickness from 0.0003” to more than 0.010”. When the adhesive is coated directly onto a release film, this is called an unsupported PSA transfer film. Common post-production processes include die cutting and laser cutting for later use in component assembly and automated pick-and-place solutions for difficult-to-apply parts and materials.[7]

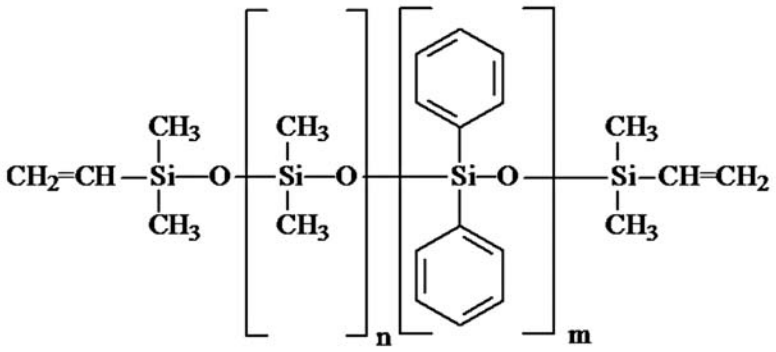
Silicone PSAs are not without their drawbacks. As stated previously, most PSAs are dispersed in a solvent system to provide viscosity control. The solvent can be problematic and limiting in transdermal drug delivery systems. Environmental concerns regarding Volatile Organic Compounds (VOCs) and plant-safety initiatives are costly factors that must be considered. In addition, solvent systems are dynamic, because evaporating solvent can impact viscosity, leading to process variations. PSAs can also limit the transdermal system design, as these materials are typically used in multilaminate, reservoir designs. PSAs that utilize peroxide systems, as mentioned previously, require an elevated temperature and may negatively impact active agents. This limitation may require that the PSA is processed in a separate step.

SILICONE GEL TECHNOLOGY

Silicone gels share the same basic siloxane polymer chemistry as silicone PSAs but lack the silicone resin credited with supplying adhesive strength to the system. Silicone gels are typically composed of two types of siloxane polymers: vinyl-functional polysiloxanes and hydride-functional polysiloxanes. Silicone gels are low-viscosity materials

FIGURE 2

A Divinyl-Terminated Diphenyldimethyl Polysiloxane Structure can be Easily Altered & Optimized for Specific Compounds



that are not dispersed in solvent systems. These materials do not contain reinforcing fillers, such as silica or silicone resins, found in silicone elastomer systems. As a result, they offer little tensile or tear strength but are extremely soft and compliant. Typically, gels used in thin-film applications use reinforcing fabrics to add strength.

The tack and adhesion of silicone gels have been proven in several transdermal, adhesive-type applications. The testing discussed later in this article illustrates the superior tack properties of silicone gels compared to silicone PSAs. Pfizer's Scar Solution® and Smith & Nephew's Cica Care® are OTC examples of silicone gels used in transdermal applications to treat hypertrophic and keliod scarring.

Silicone gels cure in the presence of platinum catalysts to solid forms that do not flow. Gels can be formulated to cure at low temperatures, which may be ideal for pharmaceutical agents that are unstable at higher temperatures. These materials can be utilized in multilaminate, reservoir or monolayer drug-in-adhesive delivery systems.

COMPARATIVE ADHESIVE PROPERTIES

The aforementioned discussion provides some basic differences between silicone PSAs and gels—from chemistry to supplied forms. The following data was compiled to determine the key property differences between silicone PSAs and gels (and differences in silicone gels with dissimilar compositions). The study acknowledges that other silicone manufacturers produce PSAs and gel technology, but the purpose of the results further on is to demonstrate the differences between NuSil's current technology offerings. In addition, the formulation compositions of the tested materials as previously described are known to the authors and are important to the discussion. The two properties tested in this study were 90-degree peel strength (NuSil Technology Test Method TM087 Reference ASTM D1876) and tack testing (NuSil Technology Test Method TM103 Reference ASTM D429 Method D).[8] Because pressure-sensitive system properties are influenced by the thickness or amount of adhesive, care was taken to ensure identical amounts of silicone were used. The materials were prepared per the applicable test method and specific material cure recommendations. Four materials were tested, and Table 1 describes the material and characteristics. The testing was performed in triplicate for each material, results appear in Table 2.

CONCLUSIONS & OBSERVATIONS

The discussion and data presented provide transdermal drug delivery system designers with another choice in pressure-sensitive-type, silicone-based adhesives. Silicones' historic healthcare use and drug solubility make both silicone PSAs and tacky gels good candidates for certain drug delivery applications. From the data, it is apparent silicone gels offer higher tack, but lower peel strength, than PSAs. It can also be concluded that gels containing phenyl functionality provided higher tack and peel results than the dimethyl gel. When considering these results, alongside factors such as drug-release rates, VOC elimination, and reservoir/matrix delivery designs, it is clear that, no matter which chemistry you choose, tradeoffs must be expected.

Table 2. Test Results.

Material Name	Peel Strength Mean (lbf/in)	Peel Strength Standard Deviation (lbf/in)	Surface Tack Mean (psi)	Surface Tack Standard Deviation (psi)
MED-1356	14.7	0.1	2.5	0.8
MED-1356 (peroxide-catalyzed)*	4.4	0.3	3.4	1.1
MED-6340	1.3	0.0	5.0	2.1
GEL-9502-30	1.4	0.2	8.2	2.5

** MED-1356 product is not supplied as a peroxide-cured product*

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pH- Independent Release From Verapamil Hydrochloride-Coated Tablets

By: Munish Kumar Dhiman, MPharm; Amit Chivate, MPharm; and S.S.Poddar, PhD

ABSTRACT

Weakly basic drugs or their salts demonstrate pH-dependent solubility. Thus, release from oral solid dosages decreases with increasing pH-milieu of the gastrointestinal tract. The aim of this study was to overcome this problem and to achieve pH-independent release of verapamil HCl from tablets. The approach used here to solve the problem of pH-dependent release of a weakly basic drug was the inclusion of succinic acid to tableting core followed by coating of tablets with polymethacrylates. Presence of organic acid within the tablet was found to maintain low pH values during drug release in pH 1.2 as well as pH 6.8 media, resulting in pH-independent *in vitro* release of the model drug. Quantity of succinic acid, coat formulation, and proportion were optimized for the desirable drug release.

INTRODUCTION

Chronic illness is often treated with medication that involves multiple daily doses, sometimes exceeding three times a day for a relatively prolonged duration. Patient compliance, and therefore efficacy of therapy, might be improved by the use of an extended-release formulation.[1]

Many drugs are weak bases or salts thereof and thus demonstrate pH-dependent solubility in the pH range available in gastrointestinal tract. At the low pH found in the stomach, weakly basic drugs are freely soluble resulting in higher dissolution rates. However, this rate decreases and sometimes even significantly when the dosage form has been transferred to the high pH region of the small intestine. With usual sustained-release (SR) dosage forms, a possible pH-dependent release could result in *in vivo* variability and bioavailability problems.[2]

Therefore, the use of pH adjusters, ie, organic acids of sufficiently low pka values, have been described by many authors for the design of SR formulations due to their ability to create an acidic microenvironment inside the dosage form.[2-5] Without such acids, when the pka value of the weakly basic drug or the pH value at which precipitation occurs would be exceeded by the pH of intestinal fluids, precipitation of the drug would take place within the dosage form. Precipitated drug being no longer capable of release, its therapeutic efficacy would be doubtful.[3] By maintaining a low pH value within the core, a constant drug release can be achieved over a wide pH range of gastrointestinal milieu.[3] Two important versions are matrix and coated units. Not much work has been reported on the coated type. Thus, the objective of the present work was to achieve a pH-independent sustained release of a weakly basic drug, verapamil hydrochloride (VHC), in association with succinic acid (SA) from release-retard polymer-coated tablets.

MATERIALS & METHODS

Verapamil hydrochloride was obtained from Nicholas Piramal India Ltd., Mumbai. Eudragit RSPO and Eudragit RLPO were gifted by Degussa Pharma Polymers, Germany. Polyethylene glycol 4000 (PEG 4000), triethyl citrate, and succinic acid were obtained from SD Fine Chemicals, Mumbai. Microcrystalline cellulose (Vivacel-101®) was obtained from J. Rettenmaier & Sohme Gmbh. Magnesium stearate, was obtained from Research Lab Chemical Corporation, Mumbai. The other ingredients utilized were of analytical grade.

Solubility Determination

Solubility of VHC in different pH ranges has been documented, which is >150 mg/ml at pH 1.2 and 2.7 mg/ml at pH 6.8.[2] Solubility of succinic acid at 37°C was determined gravimetrically, which was found to be 58 mg/ml at pH 1.2 and 107 mg/ml at pH 6.8.

Tablet Preparation

Tablets containing 120 mg VHC (batch size, 250 tablets) were prepared using microcrystalline cellulose (MCC) and SA by direct compression (DC) (Table1). Methyl red was included to monitor the microenvironment pH. Hardness was kept at 6 kg/cm^2. Compression was carried out on a 10-station rotary machine (Jaguar, General Machinery Co., Mumbai) with 9-mm standard concave punches.

FIGURE 1

Drug Release From Coated VHC Tablets Without Succinic Acid

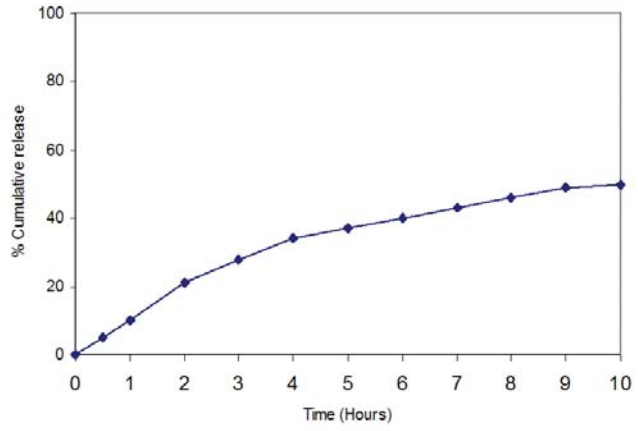

FIGURE 2

Influence of Ratio of Succinic Acid: Verapamil HCl on Release of Drug From 5.8% Film-Coated Tablets (Eudragit RSPO: Eudragit RLPO, 9:1) With 11% PEG-4000 as Plasticizer

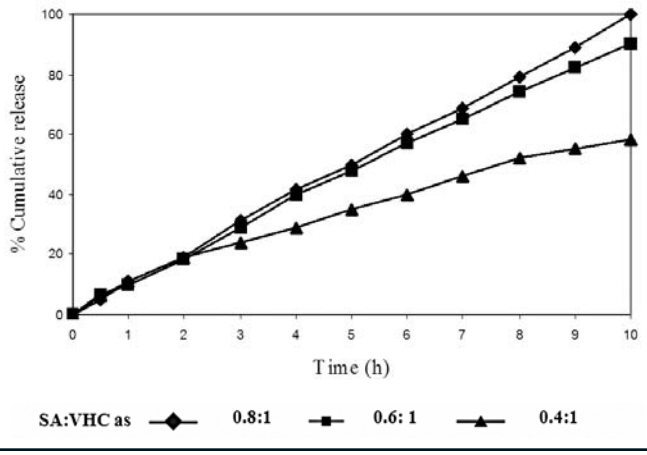

Table 1. Formulation of Tablets

Component	Batch No. & Composition (%)		
	V_1	V_2	V_3
Verapamil HCl (Drug)	30.0	30.0	30.0
MCC (Excipient)	57.5	51.5	45.5
Succinic acid (pH-adjuster)	12.0	18.0	24.0
Magnesium stearate	0.5	0.5	0.5

V_1 – Succinic Acid:Drug = 0.4:1; V_2 – Succinic Acid:Drug = 0.6:1; V_3 – Succinic Acid:Drug = 0.8:1

Coating

Tablets (batch size, 200 tablets) were film coated in a 5-inch coating pan (Erweka) by atomizing the coat solution (Spray gun 100 ml S 68; Pilot) at 10-psi pressure. Pan speed was kept at 25 rpm. Polymethacrylate (Eudragit RSPO) and polymethacrylate mixtures (Eudragit RSPO & Eudragit RLPO in various ratios) in isopropyl alcohol were used as film formers. PEG 4000 and triethyl citrate were included as plasticizers. The film composition was optimized by casting free films on a Teflon plate and then studying their properties (visual appearance and mechanical strength).

To study mechanical strength varying quantity of water was used to provide a range of downward breaking pull on the clamped film samples. The value at the break point was indicative of the mechanical strength of the films. [7]

Coating levels were represented as percent weight gain due to coat deposition on the tablets. Aliquots of tablets were taken out to represent a percent weight rise, while the coating progressed. The tablets were always dried for at least 5 min in the pan after spraying had been completed, before taking any samples or emptying the coating pan. Such withdrawn samples or batches were dried to a constant weight in a hot air oven for about 1 h at 45°C. Table 2 provides the various parameters for the coated tablets.

Dissolution Testing

In vitro dissolution performances of formulations were monitored in a 900-ml medium using a USP type 2 apparatus at 50 rpm at 37°C ± 0.5°C.[7] The media used were of pH 1.2 (0.1 N HCl) and pH 6.8 (phosphate

FIGURE 3

Dependence of Release of Verapamil HCl on Coat Proportion in Tablets

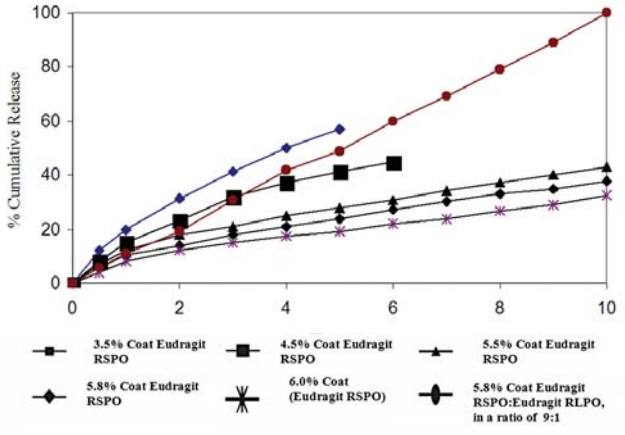

FIGURE 4

Effect of Plasticizer on Release From Coated Tablets (5.8% coat, RSPO:RLPO, 9:1)

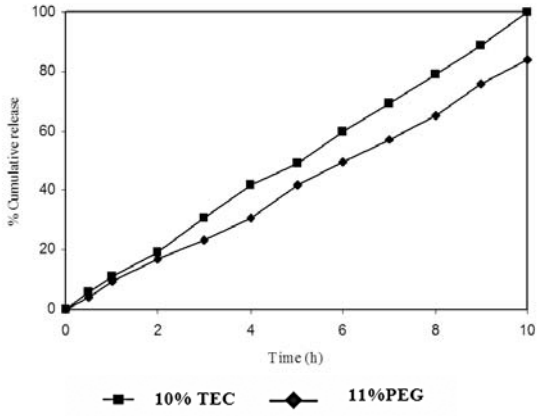

Table 2. Physical Parameters for Coated Tablets

Sr. No.	Test	Batch No.		
		V_1	V_2	V_3
1.	Hardness (kg/cm^2) (±SEM)	6-7 (±0.5)	6-7 (±0.5)	6-7 (±0.5)
2.	Thickness(mm) (±SEM)	2.25 (±0.3)	2.27 (±0.4)	2.26 (±0.4)
3.	% Weight rise (±SEM)	5.65 (± 0.03)	5.69 (±0.06)	5.67 (± 0.06)
4.	Tablet weight (mg) (Average ±SEM)	386 (±5.3)	384 (±6.2)	385 (±5.9)
5.	Assay (%) (±SEM)	101.32 (±1.21)	100.82 (±1.92)	98.35 (± 2.10)

**Mean of 6 readings (n=6), # SEM-Standard Error Mean*

buffer). Drug-release studies were performed for the first 2 h in pH 1.2 medium and for the next 8 h at pH 6.8. The speed of the paddle was set at 50 rpm. Exactly 10-ml aliquots of samples were withdrawn at 15, 30, and 60 min, followed by an hourly interval for the next 9 h. Each aliquot withdrawal was followed by replenishment with 10 ml of the medium at the same temperature. Analysis of the dissolved drug in both the media was carried out via UV spectrophotometry at 278 nm against the appropriate blank. The concentration of drug was calculated from the standard plots of drug in a pH 1.2 medium and pH 6.8 phosphate buffer, respectively.

RESULTS & DISCUSSION

Figure 1 shows drug release from coated VHC tablets without organic acid (succinic acid). Organic acid (SA) was used in an attempt to match the release rate of the weakly basic drug in pH 6.8 phosphate buffer with the release rate in pH 1.2 (0.1 N

FIGURE 5

Image of Coated Tablet After 2 Hours in pH 6.8 Phosphate Buffer

FIGURE 6

Image of Coated Tablet After 8 Hours in pH 6.8 Phosphate Buffer

Table 3. Mechanical Strength of Free Films

Sr. No.	Formulation Code	Plasticizer (%)	Mechanical Strength (g)
1.	F – 1	10	182 (±3.4)
2.	F – 2	11	206 (±2.9)
3.	F – 3	12	165 (±4.2)

**Mean of 6 readings (n=6), # SEM- Standard Error Mean*

HCl) (Figure 2). The pH-independent profiles shown in Figure 2 were obtainable for VHC. This refers particularly to the total release after 10 h, by which time SA caused the release of almost 100% of the incorporated drug.

This could be due to the creation of the consistent acidic microenvironment inside the tablets. Ideally, this acid should dissolve gradually to remain within the tablet during the entire period of proposed drug release. Independent of the pH value of the dissolution medium, the pH in the tablet core (inside the coat) was expected to be acidic and thus the solubility of weakly basic drug to be high. Organic acids have relatively low solubility in lower pH values (eg, pH 1.2) than in higher pH values (eg, pH 6.8).[2] Therefore, for further investigation of the microenvironment pH, the pH-indicator methyl red (0.2% w/w) was included in the tablet formulation to visually monitor the pH within the tablets during the time span of drug release. The indicator is red in acidic pH and yellow for pH values above 5.8.[2] VHC is soluble below pH 5.8. Thus, moving from pH values corresponding with gastric to intestinal contents; the indicator shows color change in the same pH around which solubility of VHC declines. The experiments showed that the tablet core remained red (low pH), although the color of the outer portion of the tablet slowly turned to pink (high pH but still below 5.8). Even at the end of 10 h, ie, 8 h stay at pH 6.8, there was retention of the pink color of the tablet, indicating the presence of adequate acidic microenvironment. Thus, the pH within the core of the coated tablets remained acidic, maintaining the condition conducive for solubilization and release of the drug. In the absence of a pH adjuster, as the pH within the tablet would rise, the solubility of VHC would fall, providing a reducing concentration gradient to act as a drive for the outward diffusion of the drug. Thus, eventually the release rate would fall. Construction of a suitable acidic microenvironment prevented this. The drug-release profile from the coated tablets with a composition the same as batch V_2 but containing no succinic acid is shown in Figure 1. There is a 20% release of VHC in the first 2 h, which

FIGURE 7

TS Image of Coated Tablet After 2 Hours in pH 6.8 Phosphate Buffer

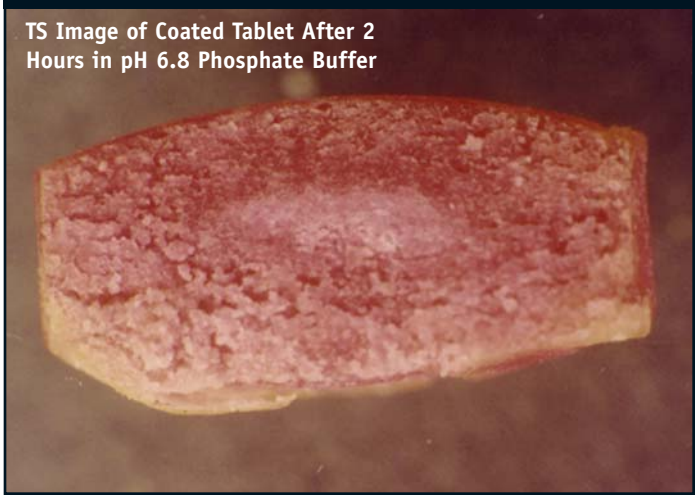

FIGURE 8

TS Image of Coated Tablet After 8 Hours in pH 6.8 Phosphate Buffer

declines as the time progresses, and only 50% VHC is released in 10 h.

To assess the effect of the amount of SA on the release properties of VHC from diffusion tablets, the proportion of SA to VHC was varied. As shown in Figure 2 (keeping the thickness of the coating of tablets the same), the effect on release was dependent on the ratio of SA and active ingredient.

As illustrated in Table 1, SA and VHC have been tried in different proportions in the formulations. An SA:VHC ratio higher than 0.8:1 led to compression and coating difficulties, while lowering this ratio below 0.4:1 could not achieve sufficient pH-independent release profiles. An SA:VHC ratio of 0.4:1 (V_1) resulted in a decreased release rate as only 55% drug was released in 10 h, while formulation with the ratio of 0.8: 1 (V_3) released drug at a slightly lower rate than 0.6: 1 (V_2), where 92% of drug was released in 10 h. This might be due to the reason that as succinic acid amount was increased, the MCC amount had to be reduced, which lead to less swelling of the tablets. An SA:VHC ratio in proportion of 0.6:1 resulted in a release rate of about 10% per h for 10 h. Thus, this composition was considered to be optimum for an effective constant release of VHC.

No doubt that SA also gets transported out of the tablet, as does the VHC. Thus, there are chances of SA getting depleted before the full exit of VHC. Increasing coat thickness may push up the drug-release retardation beyond acceptable limits. Thus, adding an adequately high quantity of SA in the tablets was the solution. It was clear (Figure 2) that by varying the proportion of SA and VHC, there was a profound effect on the release rate.

Because the release of drug through slightly swellable but insoluble polymethacrylic acid copolymers (polymethacrylates) involves the diffusion of dissolved substance through the membrane, the coat membrane thickness would exert an effect on the rate of passage of VHC.

Various coating levels of Eudragit RSPO have been tried, which included 3.5%, 4.5%, 5.5%, 5.8%, and 6.0%. Coat composition of polymethacrylates included Eudragit RSPO and 11% PEG 4000 in isopropyl alcohol. Coating to a lower percent weight rise resulted in improper coating (indicated by non-uniform distribution of coat), and there was also coat failure during dissolution. Thus, 3.5% weight rise tablets showed mechanical failure of the coat after 5 to 6 h during dissolution. Coating to a percent rise higher than 5.8% resulted in an unacceptably low release rate. With a 5.5% weight rise, there was more of a burst release in the initial 1 h than with a 5.8% weight rise. The 5.8% weight rise with Eudragit RSPO gave a release of nearly 40% drug in 10 h. While a mixture of Eudragit RSPO and Eudragit RLPO in the 9:1 ratio as 5.8% coat gave the release rate of 10% per h as shown in Figure 3.

The aforementioned change in the release rate of tablets coated with a mixture of Eudragit RSPO and Eudragit RLPO (9:1) in comparison to the Eudragit RSPO-coated tablets indicates the effect of a high permeability polymer (Eudragit RLPO) on release rate. Eudragit RSPO has lower permeability, and Eudragit RLPO has higher permeability, so a mixture of Eudragit RSPO and Eudragit RLPO could be used to achieve the desired release rate. Thus, using Eudragit RSPO and Eudragit RLPO in the ratio of 9:1 with a weight rise due to coating of 5.8 % gave the desired release rate.

With PEG 4000, at a concentration of 11% in the coat (Eudragit RSPO:Eudragit

Table 3. Mechanical Strength of Free Films

Sr. No.	Formulation Code	Plasticizer (%)	Mechanical Strength (g)
1.	F – 1	10	182 (±3.4)
2.	F – 2	11	206 (±2.9)
3.	F – 3	12	165 (±4.2)

**Mean of 6 readings (n=6), # SEM- Standard Error Mean*

Table 4. Model Fits for Different Succinic Acid: Verapamil HCL Ratio Batches Coated with Eudragit-RSPO and RLPO (9:1)

Batch No.	r^2	
	Zero-Order Kinetics	First-Order Kinetics
V_1	0.9894	0.9949
V_2	0.9992	0.7023
V_3	0.9982	0.8685

r^2 – correlation coefficient of regression lines; V_1 – Succinic Acid:Drug = 0.4:1; V_2 – Succinic Acid:Drug = 0.6:1; V_3 – Succinic Acid: Drug = 0.8:1

RLPO = 9:1), and coat itself at 5.8%, it was possible to achieve a constant release rate for 10 h as shown in Figure 4. At this plasticizer concentration, the tablets maintained their integrity in spite of noticeable swelling during dissolution. A plasticizer concentration below 11% of polymer content could not maintain the desired film strength, while a concentration above 11% resulted in inferior mechanical attributes as shown by studies on free films (Table 3).

Upon changing the plasticizer from PEG 4000 (11%) to triethyl citrate (10%) that was optimized by free-film cast studies, it has been found that there was a considerable decrease in release rate as only 85% of drug was released in 10 h. This might be due to the better pore-forming nature of PEG 4000.

To get an insight into the release mechanism for coated tablets with different ratios of SA:VHC, the dissolution profiles were plotted in various standard manners, and regression analysis was performed for each. Best fits were calculated on the basis of the correlation coefficients (r^2) determined for each of the graphical treatments and percentage deviation from zero-order release.[8]

Dissolution of VHC out of the Eudragit RSPO and Eudragit RLPO mixture-coated tablets is best described by a zero-order kinetic for the batch V_2 at a 5.8% coat level. The batch V_1 of the same coating level showed a best fit for first-order kinetic model as shown in Table 4. The percentage deviation from a zero-order release profile was minimum for V_2 as compared to V_1 and V_3 (Table 5). The studies indicated there was creation and maintenance of an acidic microenvironment by organic acids, ie, SA, for which the support was provided by the use of methyl red.

Figure 5 shows a coated tablet after 2 h in pH 6.8 phosphate buffer, showing the red color of the tablet. There was a slight color change noticed in the tablets at the end of 8 h in pH 6.8 buffer, ie, red to pink. This may be due to a fall in indicator strength due to leaching (Figure 6). To study further, the mechanism of maintenance of acidic microenvironment inside the tablets transverse sections (TS) of tablets were taken (Figures 7 & 8), showing red color and hence sufficient acid inside the core. There was no color change from red to yellow, indicating that there was sufficient SA present inside the tablet core and hence maintenance of high drug solubility even after a transition from pH 1.2 to 6.8 as dissolution progressed.

CONCLUSION

The formulation of coated tablets for pH-independent release of VHC was successfully carried out. Succinic acid:VHC in ratio 0.6:1 and coating level of 5.8% w/w of Eudragit-RSPO and RLPO (9:1) produced the pH-independent release profiles. Support for creation of an acidic microenvironment inside the tablets was provided through the use of the indicator methyl red. The formulations prepared now require animal studies for further investigations. Thus, it could be concluded that Eudragit-coated tablets with an acidic microenvironment using SA demonstrated a pH-independent release profile from the tablets.

Table 5. Percentage Deviation From Ideal Zero-Order Release Profile

Time (Hours)	% Deviation From Ideal Zero-Order Release Profile		
	V_1	V_2	V_3
0	0	0	0
1	10.00	10.00	0
2	0	0	10.00
3	14.00	0	8.00
4	24.28	4.28	1.45
5	28.88	1.10	2.25
6	31.81	0.90	4.54
7	33.84	1.54	6.15
8	34.00	2.00	7.33
9	35.88	1.76	8.25
10	38.94	2.63	9.47

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BIOGRAPHIES

Dr. S.S. Poddar is currently working as an Assistant Professor of Pharmaceutics at K.M. Kundnani College of Pharmacy, Mumbai, India. With more than 25 years of academic experience, he has 25 publications and more than 100 presentations to his credit. He earned his MPharm and PhD in Pharmaceutics from the University of Mumbai, Mumbai (India). His research interests include designing pharmaceutical dosage forms, including novel methods for modified release. He is acting as a technical advisor to various pharmaceutical companies for the development of novel formulations, scale-up, and process optimization.

Mr. Munish Kumar is a Research Scholar in the Pharmacy Department at The M.S. University of Baroda. He earneed his MPharm from the University of Mumbai, Mumbai (India) in 2003. His area of research focuses on the design and development of novel drug delivery systems.

Mr. Amit Chivate is working as Assistant Manager at Nicholas Piramal India Ltd, NDDS division at Goregaon, Mumbai. He earned his MPharm from the University of Mumbai, Mumbai (India).

Drug Delivery EXECUTIVE

Cardinal Health: Improving Quality & Efficiency in Healthcare

MR. THOMAS STUART
President,
Oral Technologies,
Pharmaceutical
Technologies &
Services segment
CARDINAL HEALTH

Cardinal Health is the leading provider of products and services supporting the healthcare industry. The Dublin, Ohio, based multinational develops, manufactures, packages, and markets products for patient care; develops drug delivery technologies; distributes pharmaceuticals, medical-surgical, and laboratory supplies; and offers consulting and other services that improve quality and efficiency in healthcare. Employing more than 55,000 people on 6 continents, Cardinal Health produces annual revenues exceeding $75 billion. Drug Delivery Technology talked with Thomas Stuart, President of Oral Technologies for Cardinal Health's Pharmaceutical Technologies and Services segment, to find out more about Cardinal Health's drug delivery capabilities and get his perspective on the future of drug delivery.

"One example of this change - extending the life cycle of a drug by launching a bioequivalent differentiated dose form - is far less likely to succeed in the future. We believe that critical stakeholders like the payor, physicians, regulatory bodies, patients, and even (for OTC) retailers are expecting better patient outcomes through meaningful innovation."

Q: Describe Cardinal Health's drug delivery business and the technologies you offer?

A: Cardinal Health is the leading global provider of drug delivery technologies by nearly every measure. We offer a broad range of both traditional and proprietary drug delivery technologies for practically every route of administration, including oral, injectable, respiratory, ophthalmic, and topical. We develop solutions for our customers' formulation/manufacturing problems. We also provide innovative, physician- and patient-preferred dosage forms, which can clinically or commercially enhance our customers' products.

Cardinal Health is the number one provider of prescription softgel capsules in the world. We offer a range of softgel options, including a recently launched plant-based product called Vegicaps® Soft™. Our other proprietary drug delivery systems include Zydis®, the gold standard for fast dissolve, and a range of modified-release technologies, including EnSolv™, EnCirc™, EnVel™, and EnGel™.

We also offer electrostatic tablet-coating technology through our relationship with Phoqus Pharmaceuticals, a U.K. pharmaceutical company. The Phoqus technology can be employed to modify a drug's release profile, and provide a unique tablet appearance for anti-counterfeiting and product differentiation, among other things.

Our topical technologies include DelPouch®, which delivers single doses of lotions, creams, or ointments, and Microsponge®, which delivers active ingredients in a sustained manner over time to reduce skin irritation.

In addition to these, we also offer more traditional controlled-release formulations and clinical and commercial supply of nearly every type of dose form on the market today.

Q: What are your newest technologies and how have they changed your drug delivery business?

A: We are focused on developing innovative solutions to complex problems and filling unmet clinical and commercial needs. A good example is the Vegicaps® Soft™ technology, a plant-derived softgel launched as an alternative to traditional softgels. With Vegicaps® Soft™, product marketers can extend a preferred patient and physician form to new patient populations who have religious, dietary, or cultural preferences. The product has been successful in the vitamin, mineral, and dietary supplement business, and we expect that it will gain further ground in the pharmaceutical market in the near future.

Our Zydis® fast-dissolve technology is the number one prescription oral fast-dissolve tablet technology on the market. Zydis® helps patients take medication easily and quickly, and can also be used to provide efficacy enhancements, such as faster onset. For some patients, it's proven to be the best way to reliably administer a drug. For example, one of our customers combined Zydis® with an innovative drug for schizophrenic patients. Their research showed that not only did the Zydis® version help bring the patients into better compliance, it also made them more compliant with other, non-Zydis® format drugs as well.

We have also gained great insight into the role that compliance-enhancing packaging plays in improving patient outcomes. We believe there are currently unmet clinical needs that would be better met by combining our advanced delivery technologies with our market-leading packaging. Our DelPouch® unit-dose topical delivery technology is a good example of the intersection of drug delivery and packaging.

Q: What are the advantages of doing business with Cardinal Health?

A: We are passionate about the pharmaceutical business and understand that each of our customers is unique with different needs. Cardinal Health can support a customer's entire range of needs, from drug discovery to commercial manufacturing to sales and marketing. We partner with hundreds of companies in the pharmaceutical industry, including both large, established companies and emerging virtuals.

In addition to the breadth and maturity of our delivery technology portfolio, we bring to our customers something unique in the drug delivery industry—unmatched insight into essentially every stakeholder that drives prescribing behavior. From physicians to retail pharmacists and from hospitals to payors, Cardinal Health participates in nearly every sector of healthcare. And we work very hard to use those relationships to generate new value for our customers. For example, we have conducted surveys of both retail pharmacists and physician customers of Cardinal Health to determine their preferences as to dose form, and the impact those preferences have on prescribing behavior. We have also made it easier for our customers to secure comparator drugs for head-to-head clinical trials.

Cardinal Health's overall financial strength and stability also give us the resources to invest in current and new drug delivery technologies and related capabilities and capacity to meet the present and future demands of our customers and their markets.

Q: What's different about drug delivery today as compared to when you started in the business in 1990?

A: What's most different is the level of increased pharmaceutical market complexity and competition. Driven by ever-changing regulatory requirements, the growing pressure from payors and more difficult drug development hurdles in general, our customers have to work harder than ever to achieve success. We are keenly aware that customers' product portfolios require a stream of continuous innovation to remain relevant and grow. That's why we work closely to understand the

complete market environment in which our partners compete, so we can best address their needs.

One example of this change—extending the life cycle of a drug by launching a bioequivalent differentiated dose form—is far less likely to succeed in the future. We believe that critical stakeholders like the payor, physicians, regulatory bodies, patients, and even (for OTC) retailers are expecting better patient outcomes through meaningful innovation.

Nowadays, companies interested in pursuing a line extension must look for a therapeutic edge or improved convenience leading to enhanced compliance or outcomes to differentiate their product. Our work with Wyeth on Advil® Liqui-Gels® is a good example of how a drug form can add value to the patient while strengthening the commercial value of the brand in the marketplace. The increased solubility from our formulation technology was shown in studies to deliver faster pain relief than competing tablet products. Through advertising and promotion of this outcome difference, Wyeth effectively has translated a clinical benefit into a meaningful point of differentiation in arguably one of the most competitive OTC markets.

We are also seeing many more drug delivery companies seeking to evolve into specialty pharmaceutical companies—with mixed results. Unless you have robust technology coupled with sufficient capability and capacity bandwidth to support both the drug delivery and the specialty pharma businesses, this can compromise the value of the delivery technology to third parties. It can also create potential conflict of interest situations, where the needs of an external partner might collide with those of an internal development program.

Q: Describe the future of the drug delivery technology business and the role Cardinal Health will play in it?

A: Technological obsolescence and competition can make this a difficult business to operate in long term. These factors have shaped our industry, and will continue to do so in the future. To stay competitive, companies have to innovate constantly and that takes resources. Like many other industries, these factors will likely lead to continuing consolidation – perhaps even accelerating in the near term.

We'll also see more cooperation between technology providers. A good example is our strategic licensing agreement with Phoqus Pharmaceuticals. We provide commercial contract manufacturing services for Phoqus' proprietary electrostatic tablet-coating process and delivery systems, and co-market these in major worldwide markets. We believe these technologies will play an important role in meeting the industry's need for anti-counterfeiting solutions and improved branding of oral medications.

As I discussed earlier, the fundamental shift in the balance of power toward payors in the United States, given a boost recently by the launch of the Medicare Part D outpatient drug benefit in January, will put increased pressure on the developers and marketers of drugs to show – and prove – improved outcomes for patients. This will impact nearly every part of the industry, including drug delivery. We believe Cardinal Health is well positioned here – our delivery technologies have a proven track record of improving outcomes, and studies show both physician and patient preference for fast-dissolving and softgel capsule forms.

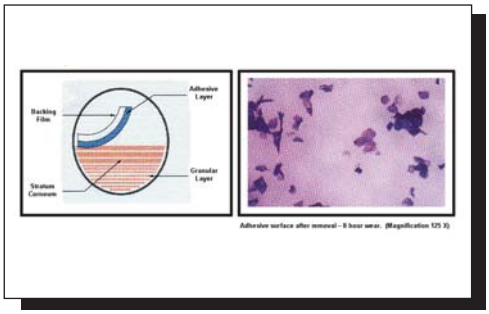
When you combine our technology, capabilities, and capacity edge with the knowledge, insights, and resources across the whole range of healthcare that we bring to the table for our customers, I believe we will be the partner of choice in drug delivery throughout the next decade. ♦

Drug Delivery Showcase

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™, EUDRACOLT™, 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 **Degussa Corporation, Rohm America LLC** at (877) 764-6872 (Option 4) or visit **www.pharma-polymers.com**

Gel Matrix Adhesive Technology

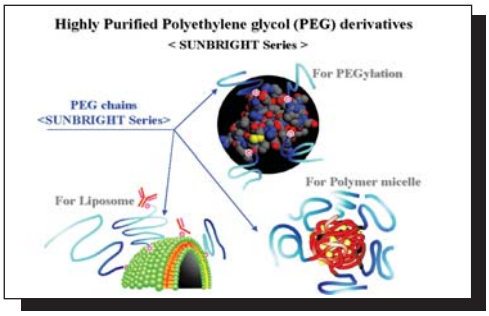


Conventional transdermal technology has relied upon traditional pressure-sensitive adhesives, which include primarily acrylate-, silicone-, and rubber- or polyisobutylene- based polymers, as the primary matrix to adhere the patch to the skin. With these traditional adhesive types, a significant amount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

Fast-Dissolve Technology

Cardinal Health's Zydis® fast-dissolve technology can help enhance a product's performance in several ways. The rapid dispersion and coating with the Zydis technology in the buccal cavity creates products that can decrease onset time, modify absorption, increase bioavailability, and augment therapeutic efficacy. Because the Zydis technology dissolves instantly on the tongue in less than 3 seconds, it can be swallowed without water. For more information, contact **Cardinal Health** at (866) 720-3148; pts@cardinal.com; or visit **www.cardinal.com/zydis**

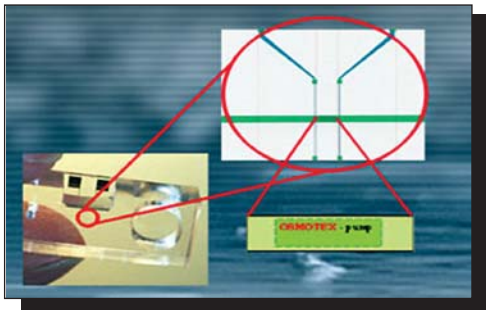
PEG Derivatives



NOF Corporation has developed excellent quality activated PEG derivatives (SUNBRIGHT Series), which are ideal for preparing pharmaceuticals and biomedical products. NOF not only manufactures various molecular weights of Methoxy-PEG with low polymer distribution, but also produces high-purity Methoxy-PEG-OH in which diol contents as impurities are claimed to be lower than any other supplier's PEGs in the world. The SUNBRIGHT Series includes polyalkylene glycols with various functional groups, which make them the most appropriate material to produce PEGylated drugs, PEGylated-Liposomes, and polymer micelles. For more information, contact **NOF Corporation** at (914) 681-9790 or visit **www.nof.co.jp/dds**

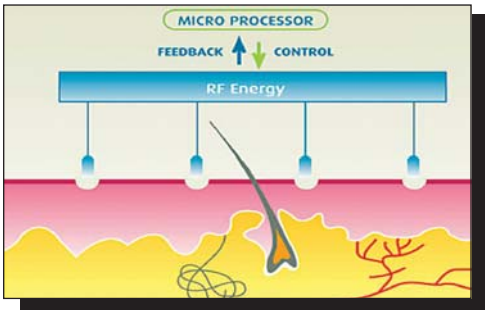
Drug Delivery Showcase

Microactuator Technology



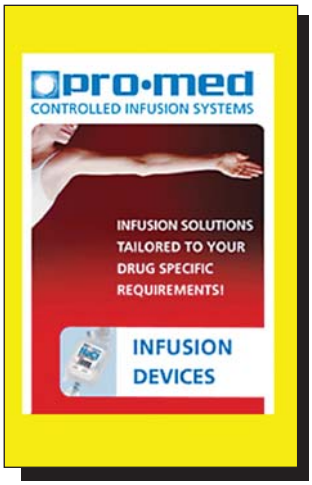
Osmotex has developed a unique electrokinetic micropump (or generally, a microactuator technology), which is extremely small - thousands of individually addressable actuators can be integrated on a microchip. The microactuator contains no moving parts, can be produced cheaply by standard microfabrication, and runs typically on 1 to 20 Volts (compared to 100s to several 1000s of Volts for competing technologies). It can pump, mix, or valve a wide range of liquids without affecting their properties, and is stable and reliable, having a long service time. Osmotex's business is to license its actuators to producers of all kinds of microfluidics end-user products. In connection with this, **Osmotex** will enter into co-development with companies to incorporate its actuators into complete MF systems. For more information, visit **www.osmotex.no**

Cell Ablation Technology



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

Controlled Drug Infusion



SmartDose® is a simple-to-use "plug & play" disposable drug delivery system, which efficiently addresses the growing needs for increased safety, improved ease of use, and cost containment in controlled drug infusion. It is a revolutionary disposable system composed of a self-powered, prefilled container with dedicated inlet & outlet ports for both closed drug transfer and drug infusion, respectively. As a pharmaceutical partner, the added value is that SmartDose® improves the handling safety and ease of use of your drug, combined with unmatched patient compliance, directly influencing your drug's acceptance and its clinical efficiency. Within the pre-hospital, in-hospital, ambulatory, homecare, emergency, or military environment, the infusion drug specifications are strictly respected - from reconstitution through to infusion. For more information, visit **Pro-Med Controlled Infusion Systems** at **www.pro-med.net**

Systems for Drug Administration

Medimop Medical Projects Ltd., a West Pharmaceutical Services, Inc., company, is a leader in the world market for transfer, mixing, and administration systems for injectable pharmaceuticals. The company designs, develops, and manufactures needleless devices and product packaging systems that safely and efficiently connect, interface, mix, and filter injectable drugs in vials, bags, ampoules, and syringes. Medimop offers a variety of products to meet drug formulation and disease-specific needs. Medimop's products offer users safer and simpler product handling, reduced medication errors, and improved patient compliance. All Medimop products are 510K approved by the United State Food and Drug Administration and carry CE certification. For more information, visit **Medimop Medical Projects** at **www.westpharma.com**

Drug Delivery EXECUTIVE

Ventaira Pharmaceuticals: Breathing Science & Technology Into Medicine

MS. LESLIE J. WILLIAMS, MBA
President & CEO
VENTAIRA PHARMACEUTICALS, INC.

"The market potential for local and systemic pulmonary drug delivery with technologies, such as Ventaira's, is huge. It is currently nearly $10 billion, and many believe that by the end of the decade could grow to in excess of $25 billion due to the increasing prevalence of asthma and COPD along with applications in other areas, such as insulin therapy for diabetes."

Ventaira is a specialty pharmaceutical company dedicated to improving current patient therapies and quality of life by providing novel pulmonary drug products in the outpatient setting. With its proprietary Mystic™ inhalation technology (Electrohydrodynamic or EHD), the company can deliver respiratory and systemically active drugs to the lung more efficiently and effectively. Drug Delivery Technology recently interviewed Leslie J. Williams, President & CEO of Ventaira Pharmaceuticals, Inc., to discuss how her company is currently developing its own proprietary inhaled drugs for the treatment of asthma and taking advantage of newly created opportunities for existing or novel drugs that may be more easily delivered via inhalation.

Q: Please describe Ventaira's Mystic inhalation device. What stage is the device in?

A: Ventaira's Mystic inhalation devices are based on a unique liquid aerosol technology called Electrohydrodynamics (EHD). This is an electronic nebulization process in which an electrical field is applied to a conductive liquid leading to the formation of a soft mist droplet aerosol. An electrical field charges the fluid's surface, resulting in the induction of repelling surface charges that overcome liquid surface tension and results in the break up of the fluid into uniform droplets. A subsequent electric field neutralizes the droplets, resulting in an expelled soft mist. The particle size characteristics of the aerosol can be controlled by adjusting the physical and chemical characteristics of the formulation, together with the flow rate and electrical field properties. In summary, the technology has the fundamental attributes of producing soft clouds of uniformly sized particles with very high efficiencies, enabling consistent delivery of drug to and through the lungs.

Our hand-held devices are not only efficient, but importantly, are easy to use. When the patient is ready to take his medication, he turns on the device and breathes normally. The breath triggers the device to deliver the appropriate dose. This makes it very easy for children, older patients, and those with compromised respiratory function who have a difficult time taking short deep breaths. There is minimal adherence of drug in the mouth and back of the throat. Our device can be used

with different types of drugs, and we have shown excellent dose-to-dose reproducibility.

As for the stage of development of our device, we will have Device Verification Test (DVT) units in Q1 2006. This means these devices are fully integrated devices with full production-molded parts and a complete battery of tests. We plan to use these devices in our Phase IIb clinical trial in the second half of 2006. We are also aggressively working on our commercial device, which is a smaller version of our production units. We expect to have functional prototypes of the commercial device the first half of 2006 and final commercial production units the first half of 2007.

Q: What differentiates Ventaira's Mystic technology from Dry Powder Inhalers (DPIs) or Metered Dose Inhalers (MDIs)?

A: We have proven that our Mystic technology can more efficiently deliver drugs to the lung, thus requiring less drug to get the same effect. In addition, by varying particle size with our formulations, this unique technology enables us to target regional lung delivery, enabling both topical lung or systemic drug delivery. Because of the soft mist attributes and uniform particle size, we have shown minimal dose-to-dose variability. Along with these features, we expect the device to be easy to use. These are improvements over other types of inhalation technologies, such as DPIs and MDIs.

MDIs and DPIs have been around for decades. These devices have a much lower delivery efficiency and have significant dosing variability. This can be due to difficulty in using the device or the inspiratory effort required of patients.

Q: What clinical programs are you currently working on, and what Phase are you in?

A: We are currently working on a program called Acuair®, which is our proprietary formulation for the treatment of asthma. Fluticasone is the active drug delivered with our easy-to-use device.

We are also currently working on a fluticasone/salmeterol combination for the treatment of asthma. This combination is very similar to GlaxoSmithKline's currently marketed drug Advair®, which may have peak sales of $8 billion. Our goal is to have our combination of fluticasone/salmeterol for use with our technology by 2010 when the initial GSK patents expire. We will look to license this program to a partner working in the asthma space.

As for what stage we are in — we have completed a Phase I clinical trial with Acuair and are currently conducting a scintigraphy/PK study. We expect the study to demonstrate the clinical application of our technology. Our plan is to complete this study in the first quarter of 2006. We then plan to initiate a Phase IIb trial in asthmatics and license the product for Phase III development and commercialization.

We are also expanding our portfolio of compounds that can be administered with this technology. These compounds span a variety of chemical classes and therapeutic areas.

Q: What is the market potential for Ventaira's technology?

A: The market potential for local and systemic pulmonary drug delivery with technologies, such as Ventaira's, is huge. It is currently nearly $10 billion, and many believe that by the end of the decade could grow to in excess of $25 billion due to the increasing prevalence of asthma and COPD along with applications in other areas, such as insulin therapy for diabetes.

As I mentioned previously, our technology is an improvement over currently available devices on the market. Mystic technology is more efficient at getting drugs to the lung and is easy for patients to use. Additionally, we have formulation capabilities that allow us to target regional lung delivery efficiently and effectively via inhalation. Our technology can potentially deliver a wide variety of small to large molecules used to treat a variety of diseases.

Q: What is Ventaira's commercialization strategy? Business strategy?

A: We plan to develop our Acuair product for treating asthma through Phase IIb and then partner for Phase III trials and commercialization. We do not have plans to become a fully integrated pharmaceutical company. We believe we are optimally positioned in the value chain by focusing on lead identification and optimization and Phase I and Phase II development.

Our business strategy is to build a specialty pharmaceutical business by utilizing our Mystic inhalation and formulation technology to develop new pharmaceutical products for inhalation. We are building value by:

- Developing a best-in-class inhalation device;
- Developing proprietary products utilizing Mystic technology; and
- Strategically partnering with pharmaceutical companies interested in licensing "super" generics; life cycle management of their own drugs; and using inhalation as a mode of delivery for their new chemical entities (NCEs).

Our Mystic inhalation and formulation technology are supported by a comprehensive portfolio of patents and technical know-how.

Q: The pulmonary drug delivery field has seen significant advances in the past 5 years, where do you see this field going?

A: I believe there is tremendous growth opportunity in the pulmonary drug delivery space. The prevalence of asthma and COPD continues to grow along with the demand for improved treatments. Of growing interest is using the huge surface of the lung as a portal for systemic drug delivery. Systemic applications hold enormous potential. It is a very exciting time for those of us working in this field because the drug Exubera, inhaled insulin, developed in partnership between Nektar and Pfizer is expected to be approved in the US late 2006. This is a major breakthrough for using pulmonary inhalation for treating systemic disease. The critical factor determining the success of systemic pulmonary drug delivery is the ability to reach the deep lung. The challenge is to produce a fine mist or powder comprising uniform particles of small diameter, 2 to 5 micrometers, and to deliver it as a well dispersed cloud at the right speed to reach the alveoli. Some estimate that if an inhaler can prove that it can deliver drug deep into the lung and deliver systemic drugs, the market for such an inhaler could reach in excess of $25 billion a year. The field is growing rapidly, and it will continue as we get further experience. Pulmonary inhalation of drugs, such as insulin, is likely to be a welcome advance for patients whose only alternative at this time are injections.

Q: The FDA has strict guidelines in place for delivering drugs via inhalation. Please describe these restrictions and how Ventaira's device meets these guidelines?

A: It has been difficult to get new inhalation drug products approved. Usually this difficulty is due to performance limitations of the device component and not clinical limitations related to the drug substance. For example, the device may not be able to consistently pass the FDA's expectations for Dose Content Uniformity, meaning the same dose is delivered each time the inhaler is used. I don't foresee any changes in the regulatory environment or expectations related to this. The FDA will continue to expect the device to perform reliably over a range of anticipated environmental conditions. I expect the FDA's device performance expectations will be consistently applied across different review divisions as more applications are filed for non-respiratory clinical objectives, such as insulin. We have demonstrated that Ventaira's Mystic technology meets these requirements.

Q: What are the next steps for the company and its technology?

A: We have a busy 2006 planned. First and foremost, we will remain focused on bringing our device to completion – demonstrating manufacturability and commercializability. We also plan to demonstrate the application of the technology in patients with our lead compound. We plan to have our DVT device available by the first half of 2006 as well as completion of a scintigraphy/PK study by the second quarter of 2006. Then, if all goes well, we will initiate our Phase IIb efficacy study for the treatment of asthma. Our commercial device will be available by the first half of 2007, and we plan to have our fluticasone/salmeterol formulation for treating asthmatics ready for clinical trials. We are also advancing our overall formulation space as well, and our goal is to design two additional base formulations to the EHD spray space.

Q: In your opinion, what are the biggest challenges you and your company face?

A: I think the biggest challenge we face is reducing the device technology into practice. By this I mean demonstration that the device can be built at the right size with the intended components and that it works properly through the intended dosing regimen and shelf life. It is easy to get carried away with prototypes that look promising but are not a practical execution of the intended design. However, we are already on our way achieving this. By the middle of 2006, we will have our final production design complete. We have an experienced team that is committed to assuring that we have an effective, efficient, and easy-to-use device. ♦

QUICK-DISSOLVE FILMS

Quick-Dissolve Strips: From Concept to Commercialization

By: Caroline M. Corniello

INTRODUCTION

Watson Inc. has been manufacturing water-soluble films for more than 40 years. Mr. John Watson, a water-soluble film pioneer, envisioned supplying his added value ingredients to his bakery customers in a novel delivery system called Sol-U-Paks™. Sol-U-Paks were designed from a cold water-soluble polymer, hydroxypropylmethylcellulose (HPMC), and were intended to be used as a unit-dose delivery system. This ensured that the consumer would be able to consistently add the ingredient to a batch with accuracy, and the batching operator would not be exposed to the added value ingredients. Using a vertical form, fill, and seal machine, the cold water-soluble Sol-U-Paks would be filled at Watson Inc. with the customer's ingredient. Next, the company would ship the package to the customer, and the batching operator could then immediately add the Sol-U-Pak to the batch.

In the past 5 years or so, the US consumer has come to accept these water-soluble films as a novel delivery system called Quick-Dissolve Strips. Quick-Dissolve Strips are a convenient way to deliver active pharmaceutical ingredients (APIs) to the consumer because they are easier to swallow, as the filmstrip dissolves in the oral cavity before ingestion. No water is needed for the filmstrips to dissolve, so this is an added convenience for the consumer. Water would be needed if the API were to be delivered using the traditional tablet/capsule delivery system. Quick-Dissolve Strips are also an improvement over elixirs, which are messy and difficult to dispense with accuracy.

The primary focus of this article is to review some of the physical attributes needed to design a Quick-Dissolve Strip to ensure consumer acceptance. A secondary discussion will focus on a different water-soluble film, which is intended to deliver the API vaginally. Finally, taste-masking and mouth-feel techniques used to design caffeine and benzocaine Quick-Dissolve Strips will be discussed.

FILM CHARACTERISTICS & PROPERTIES

Normally, most consumers are expecting to see a consistent looking Quick-Dissolve Strip that is stiff, flat, and doesn't curl on the edges. For consumer acceptance, the water-soluble filmstrip must be robust enough to be removed from the unit-dose packaging without breaking. The strip must also dissolve readily in order to deliver the API rapidly when placed on the tongue, so that a gummy texture is avoided. The most important component in the film matrix, which can achieve these characteristics, is to choose the correct polymer system. For example, a Quick-Dissolve Strip designed using polyethylene oxide (PEO) as its polymer would be a poor choice due to the lubricous nature of this polymer. The lubricous nature causes the filmstrip to become gummy in the mouth, which in turn causes an unfavorable mouth-feel for most formulas. However, most of the other film characteristics can probably be obtained. On a favorable note, PEO is an excellent choice when considering an application like a whitening strip. This is due to the mucoadhesive nature of PEO, which will enable the polymer to stick to the gum line for an extended period of time.

In stores today, consumers can find Quick-Dissolve Strips that have been made from the following polymers: pullulan, starch, HPMC, HPC, sodium alginate, pectin, and CMC. By carefully balancing the mechanical properties, solubility rate, taste, and mouth-feel (texture) for the filmstrip, these polymers can be employed to design Quick-Dissolve Strips.

Due to the inverse proportional relationship between mechanical properties and solubility rate, these two properties must be carefully balanced when designing a Quick-Dissolve Strip so that the stiff filmstrip can be efficiently cut to size, and filled into unit- dose packaging while still having rapid dissolution. By controlling the molecular weight distribution (MWD) of the film matrix, these two properties can be

Table 1. General Trends of MWD Affects on Physical Properties of Filmstrips

Physical Property	Low MWD Polymer	High MWD Polymer
Viscosity of Solution	Low	High
Solubility Rate of Filmstrip	Rapid	Slow
Stress – Strain Behavior	Brittle Filmstrip	Flexible Filmstrip

optimized. Table 1 shows some general trends of how the MWD of a polymer will affect various physical properties of filmstrips. Usually, when designing Quick-Dissolve Strips, a polymer with a low MWD or viscosity, such as HPMC E5 or pullulan PI-20, is employed. When the desired physical properties aren't obtainable using a single low viscosity polymer, mixing various viscosity grades of the polymer may overcome this problem. When mixing a high viscosity polymer with a low viscosity polymer, the Quick-Dissolve Strip will generally have mechanical properties similar to the higher MW polymer, and the solubility rate will be similar to the lower MW polymer. When optimizing these properties, two of the same polymers can be employed or they can differ.

VAGINAL FILMS

For a project where the API is going to be delivered to the vaginal area, a very different water-soluble film matrix is desired. A common characteristic of this film will be the need to dissolve rapidly in the vagina; however, the mechanical properties will be quite different for the vaginal delivery film. This film needs to be flexible and tough enough so that when folded into quarters, the film can be inserted into the vagina without breaking. Another characteristic of the vaginal delivery film is that after dissolving, the film must go undetected by the consumer. Low viscosity, 88% hydrolyzed polyvinyl alcohol (PVA), is an acceptable polymer for this application because this polymer exhibits a balance of flexible and tough stress-strain behavior with rapid solubility at 37ºC. Polyvinyl alcohol is an interesting polymer because of its ability to hydrogen bond. The hydrogen bonding of the 88% hydrolyzed PVA material allows for excellent mechanical properties when compared to other polymers at the same viscosity that aren't capable of hydrogen bonding. In recent years, this polymer has been approved by the FDA as a GRAS ingredient with limited-use levels in the supplement arena; therefore, there probably will be innovative Quick-Dissolve Strips designed using this polymer in the future.

CHALLENGES

It is challenging to incorporate pharmaceutical actives into Quick-Dissolve Strips for several reasons. First, there is limited space available in the film. Currently at Watson, the maximum amount of API that can be incorporated is approximately 30% of the film matrix's composition. Therefore, this delivery system is not suitable for all APIs. Because most Quick-Dissolve Strips are limited to a specific width (0.875 in) and length (1.25 in) due to the size of the oral cavity, we will discuss changing only the thickness in this article. If desired by the customer, Watson can vary the other two dimensions, depending on the application.

By increasing film thickness, the weight per strip will increase; therefore, the load of the API will increase proportionally for the same film matrix. Table 2 provides examples on how increasing film thicknesses can deliver a higher load of API per filmstrip. To date, there are Quick-Dissolve Strips on the market that weigh up to 100 mg (due to an increase in filmstrip thickness) and can thus deliver up to 25 mg of API per filmstrip. A negative impact of increasing the film thickness is that the solubility rate increases. If one of the other dimensions were increased instead, the impact on solubility is not as great; however, the filmstrip may not fit comfortably in the consumer's mouth. For some applications, it may be acceptable to deliver higher loads of API by instructing the consumer to take multiple strips per day.

For consumer acceptance, there is a limited amount in which the solubility rate can be increased because the slower dissolution rate will usually cause the filmstrip to feel gummy in the oral cavity. If the filmstrip needs to dissolve slowly over a prolonged period of time, then the film matrix needs to be designed in such a manner that a gummy mouth feel is avoided. Watson Inc. has designed some filmstrip systems in which a gummy mouth feel is avoided when the dissolution rate is increased for a prolonged period of time, so that the product is acceptable to most consumers. Additional work needs to be completed before it's determined whether the API is also delivered over a prolonged period of time in the oral cavity.

Caffeine

Designing Quick-Dissolve Strips is also challenging because the bitter taste of the API must be overcome. In our development efforts,

Table 2. Effect of Film Thickness on Amount of Active Delivered Per Filmstrip

Filmstrip Thickness (mil)	Weight of Filmstrip (mg)	Amount of Active Per Filmstrip (mg)
2.0	52	15.6
2.2	58	17.4
4.0	104	31.2
5.0	130	39

we were able to design Caffeine Quick-Dissolve Strips that contain 16 mg of caffeine per each 58-mg filmstrip. For this project, overcoming the bitter taste of caffeine was difficult because the filmstrip contained approximately 30% caffeine. In order to obtain a pleasant-tasting product, a variety of taste-masking aids were employed. Primarily, the flavor chosen must complement the bitter off-notes of the active; therefore, a flavor with menthol is the most promising selection to be matched with caffeine because menthol distracts from the organoleptic effects of the bitter taste. Secondly, with the right balance of sweeteners, the perception of bitterness can be minimized. For this project, a sweetener that is detected late in the flavor profile is preferred, because the lingering sweetness masks the bitter notes. Thirdly, bitter-blocking aids can also be employed. For this particular active, all three techniques were employed to meet the objective of designing a pleasant-tasting Caffeine Quick-Dissolve Strip. In an independent study, Dr. Roger E. Stier from Noville Inc. reports using similar techniques when masking the bitter notes of caffeine and Lipitor.[1]

Watson Inc. has explored encapsulating the active API as a means to minimize the detection of bitter flavor and has determined that several factors must be considered to do so. Encapsulating the active will expose the API to two manufacturing processes that can have a negative impact on stability; therefore, extensive testing will need to be conducted to ensure product integrity. Another consideration is that the material used to form the encapsulation must also be stable through the film manufacturing process, which is typically a high moisture environment with elevated temperatures. The bitter notes will be detected in the filmstrip if the encapsulation doesn't hold up to the film manufacturing process. Furthermore, because there is a limited amount of available space for this delivery system, diluting the matrix with the encapsulation material can further limit the amount of API in the Quick-Dissolve Strip.

When the customer considers these factors and determines that optimizing flavor requires the API to be encapsulated, Watson Inc. will need to carefully choose the encapsulation material. The company will also need to further optimize the manufacturing process to limit the degradation of the API and to ensure the integrity of the encapsulation. More than likely, further testing will need to be conducted on the Quick-Dissolve Strip to ensure that the active is released from the encapsulation material into the digestive track at the correct time, and that the API is biologically available in the same manner as currently approved by the FDA; otherwise, clinical trials will need to be conducted.

Benzocaine

For a Quick-Dissolve Strip that contains benzocaine, the challenge to balance the flavor is quite different. In this case, the benzocaine numbs the taste receptors so quickly that in certain formulas, the flavor can go undetected, and the consumer only feels numbness. One way to overcome this problem is to use sweeteners that release quickly in the flavor profile so that the flavor is developed before the consumer detects the numbing effect. Another way to obtain the desired balance of flavor is to design a filmstrip that releases the flavor quickly, while following with a slow

release of the benzocaine. For example, a Quick-Dissolve Strip can be designed by sprinkling an encapsulated flavor onto the surface of the film matrix before drying the filmstrip. By doing this, the fast- dissolving encapsulated material will release the flavor before the slower dissolving filmstrip can release the benzocaine.

SUMMARY

In this article, Watson has discussed some of the key physical attributes needed to effectively design a Quick-Dissolve Strip so that there's a balance of mechanical properties, solubility rate, flavor profile, and mouth feel, which must be achieved in order to ensure consumer acceptance. As a first step, the materials and lab equipment needed to design each project are carefully chosen once the application is well defined by the customer. By outlining the project goals and understanding the unique customer requirements, each goal can be met in a timely and cost-effective manner. Furthermore, as various formulas are investigated, the data is collected and skillfully interpreted to choose effective direction and targeted product specifications. When the customer approves a formula and the target product specifications, a pilot run is performed so that additional equipment needed is identified and purchased to optimize the manufacturing process. Next, a protocol is written so validation work can be executed in accordance with the customer's specified needs, and finally, a report is written so that the formula can be commercialized.

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BIOGRAPHY

Ms. Caroline M. Corniello is the Director of Product Development in the Film Technology Division of Watson Inc. She earned her BS in Chemistry from Southern Connecticut State University and her MS in Polymer Science from the University of Connecticut. Ms. Corniello joined Watson in December 2002 with several years experience in developing and manufacturing water-soluble films in a commercial environment. At Watson, she is currently researching and developing the applications of pharmaceutical-grade films in cosmetics and drug delivery.

MICELLAR NANOPARTICLES

Micellar Nanoparticles: A New Drug Delivery Platform

By: Rahul Singhvi, ScD, President & Chief Executive Officer, Novavax, Inc.

INTRODUCTION

Transdermal delivery involves application of a pharmacologically active compound onto the skin to achieve therapeutic blood levels in order to treat diseases remote from the site of application. Ever since the approval of Transderm-Scop®, the first transdermal drug delivery system (TDDS) in 1981, there has been explosive research in the field of transdermal therapeutics for treatment of a variety of clinical conditions. Unmatched clinical benefits, profound industry interest, existence of strong and niche markets, and regulatory precedence show why TDDS has become a flourishing and viable dosage form. The current transdermal therapeutics market is segmented into traditional formulations like gels, advanced delivery systems, such as patches, and novel physical technologies like microporation, iontophoresis, and sonophoresis. Transdermal delivery offers controlled disposition of the drug into the patient leading to a steady blood-level profile, and offers reduced systemic side effects and improved efficacy over conventional dosage forms in certain cases. Transdermal delivery is particularly advantageous for those drugs having significant hepatic first-pass metabolism or degradation in the GI tract. Throughout the years, the US FDA has approved more than 40 transdermal products, spanning about 15 molecules, which amounts to nearly $2.5 billion.

Micellar nanoparticles (MNP) is a nanotechnology-based formulation that has achieved a breakthrough in transdermal therapeutics. It represents a robust and versatile delivery system that can accommodate a range of therapeutic compounds having varying physico-chemical properties.

MICELLAR NANOPARTICLES: A PRIMER

Micellar nanoparticle (MNP)-based emulsions (lotions) are attractive alternatives for systemic drug delivery via topical application. The technology allows high concentrations of drug to penetrate the skin and functionally create a drug depot in the stratum corneum and epidermis. This route of delivery provides similar advantages of patch technology in avoiding both contact with the GI tract and hepatic first-pass effects, and it is cosmetically more acceptable to many patients. MNP drug delivery offers a potentially fast and inexpensive pharmaceutical development model by using drugs already proven safe and effective to create new proprietary formulations.

The active ingredient is distributed within the formulation in different physical forms micro/nanocrystals (or particles), solution form in hydro-alcoholic/oil droplets, and micellar-associated form (Figures 1a and 1b). MNP represents a multi-phase dosage design with the active ingredient in readily available solution form as well as in long-acting particulate depot form.

ADVANTAGES OF AN MNP-BASED PRODUCT

Though currently available commercial topical dosage forms like gels and patches successfully drive the drug into the systemic circulation, they present some drawbacks. The gels need to be applied over a large area of skin, and the composition may lead to skin dryness in certain cases. The patches have very limited surface area for drug transport leading to accumulation of drug in high concentrations beneath the applied area, which can result in significant skin irritation. Additionally, many people are

MICELLAR NANOPARTICLES

FIGURE 1A

Freeze-Fracture Microscopic Image of Estrasorb Showing Emulsion Droplet Embedded in Micellar Matrix

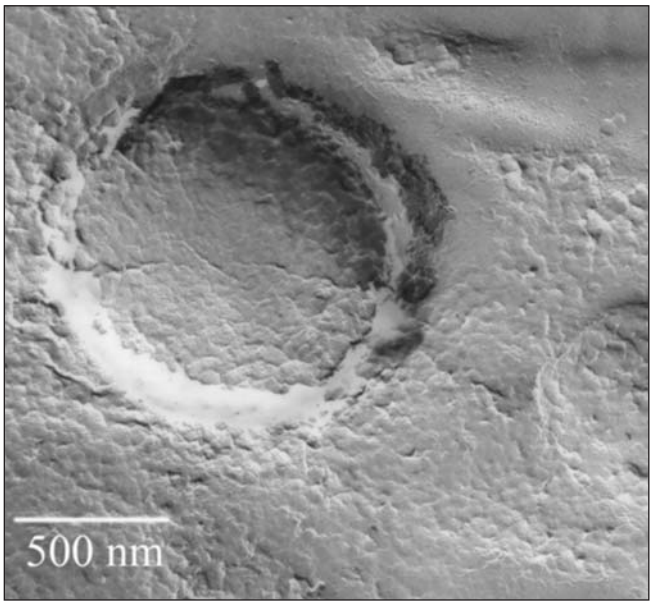


FIGURE 1B

Transmission Electron Microscopic Image of an MNP Preparation Showing Nano-Structured Emulsion

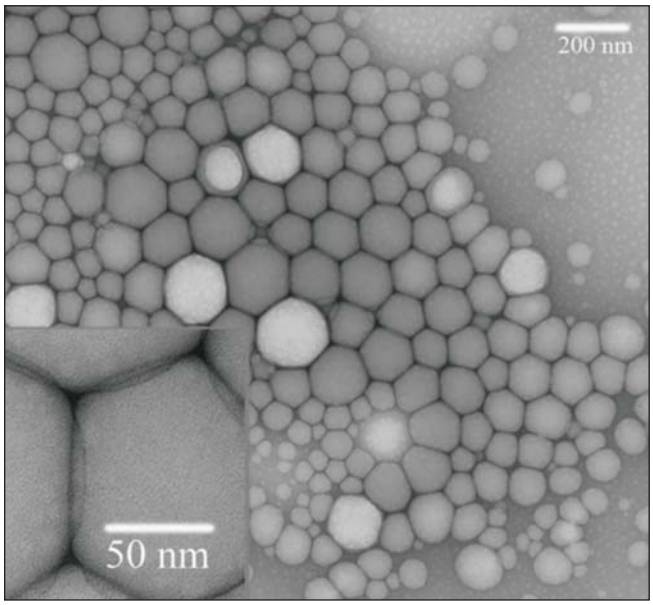


Table 1. Salient Features of MNPs

- Topical dosage form for systemic delivery of pharmaceuticals
- A unique nano-structured vehicle composed of nano-sized particles/droplets dispersed in a liquid crystalline matrix
- High drug loading capacity
- The formulation utilizes excipients generally regarded as safe (GRAS) for humans by the FDA
- The composition promotes quick penetration of drug into the skin without causing irritation/tissue damage
- Utilizes proprietary high shear mixing process for manufacturing, offering improved product stability
- Robust and versatile delivery system for a range of therapeutic compounds
- Excellent bioavailability for many drugs showing significant hepatic first-pass
- MNP technology – best suited for lipophillic small molecules
- The intellectual property behind the MNP technology is protected by worldwide patents

allergic to the adhesives used in patches. They are also most expensive among the marketed transdermal products.

MNP is the flagship delivery system developed at Novavax that is evolving as an innovative transdermal dosage form that negates the drawbacks presented by gels and patches.

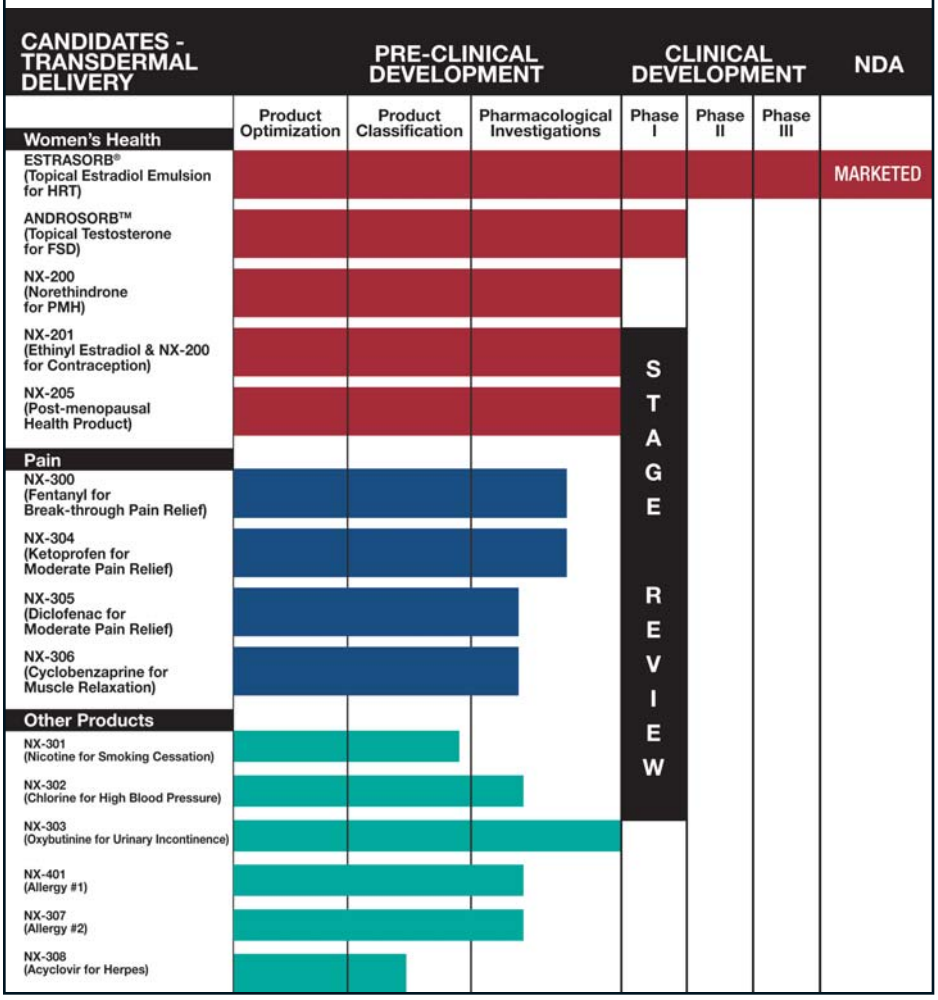
MNP technology has been applied for estrogen replacement therapy with 17ß-estradiol in Estrasorb®, the company's first internally developed FDA-approved product (Figure 2). Estrasorb is a nano-engineered topical dosage form that is approved by the FDA for hormone replacement therapy. Estrasorb has been a revolutionary product in nanotechnology-based pharmaceutical product development that redefines transdermal therapeutics. Estrasorb validates MNP technology and is the only emulsion-based formulation in the topical estrogen replacement market.

FIGURE 2

Estrasorb® - First Commercially Available Product Based on MNP Technology

FIGURE 3

Product Development Pipeline at Novavax Based on MNP Technology



PRODUCT PIPELINE BASED ON MNP TECHNOLOGY

Novavax has multiple projects in its drug delivery pipeline, which are focused on projects that are compatible with MNP technology and target large, unsatisfied markets (Figure 3). Currently, the company's focus is on topical delivery, but it believes its technologies may have broader applications.

Several small molecular weight compounds have been evaluated to prove the versatility and expandability of the MNP technology. Preliminary studies (Figures 4a through 4e) highlight the following findings:

- Technology extends to non-hormonal, small molecular weight compounds;
- There is a rapid onset of action (see fentanyl graph), the formulation can be easily optimized to tune this phase;
- A longer duration of action (drug depot) exists, ranging from approximately 18 to 36 hours after single topical application, sustained-release formulation;
- Maintenance of steady plasma drug levels is achievable on multiple dosing (unpublished results) within therapeutic window; and
- There is a possibility of administration of drug combinations for improved therapeutics (unpublished results).

MICELLAR NANOPARTICLES

FIGURE 4A

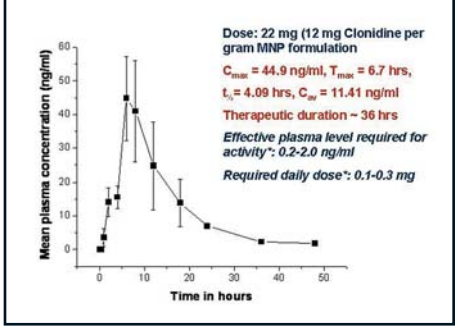


FIGURE 4B

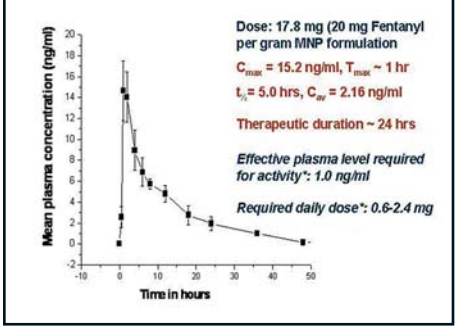


FIGURE 4C

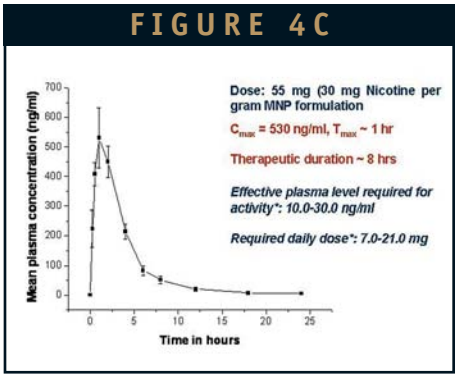


FIGURE 4D

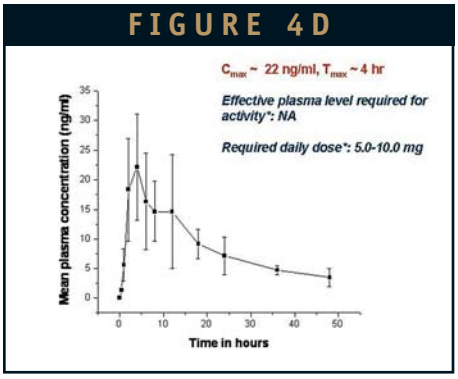
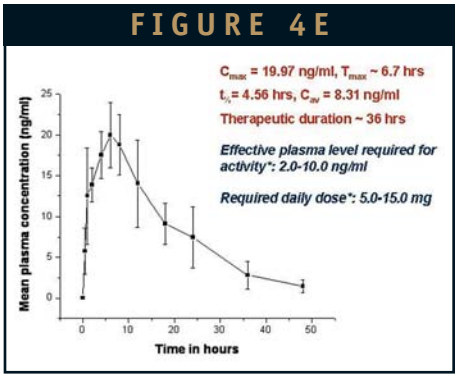


FIGURE 4E



Plasma Distribution Profile of Investigational Compounds Formulation in MNP

SUMMARY & OUTLOOK

Transdermal drug delivery is not suited nor clinically justified for all drugs, yet it is viewed to be much more limited than it actually deserves. MNP technology helps to incorporate and deliver many therapeutic compounds that are otherwise viewed as unsuitable for transdermal delivery. The MNP technology allows fast, low-cost product development compared with typical development of new chemical entities. From proof-of-principle in a validated preclinical model through advancing into a Phase I study in humans requires approximately 12 months to complete. The data from Novavax's preclinical studies show high probability of clinical success within a shorter development time horizon and a lower cost than a typical NDA. The results expand the product opportunities for Novavax into attractive therapeutic categories, such as pain, urology, and allergy. Novavax filed two INDs with the FDA at the end of 2005 for two non-hormone product candidates.

BIOGRAPHY

Dr. Rahul Singhvi was appointed President and CEO of Novavax in August 2005. He joined the Company in 2004 as Vice President, Pharmaceutical Development and Manufacturing Operations and was appointed Senior Vice President and Chief Operating Officer in April 2005. He is charged with restructuring the company to focus on its core competency of new product development and innovation and drive shareholder value. Prior to joining Novavax, Dr. Singhvi spent 10 years with Merck & Co, most recently serving as Director of Vaccine and Sterile Operations in the Merck Manufacturing Division. In this position, Dr. Singhvi was responsible for operating a manufacturing unit producing a new biological product and initiating the start up of a second biological product manufacturing unit. In addition to his functional expertise within process development and manufacturing, Dr. Singhvi was a recognized leader within Merck & Co., Inc. for the depth and breadth of his expertise, and led several cross-functional teams responsible for technology transfer and development of new products. Dr. Singhvi holds several patents in the area of cell culturing systems and has co-authored numerous publications, book chapters, and abstracts on biochemical engineering and cell physiology. He earned both an MSc DSc in Chemical Engineering from MIT, Cambridge, an MBA from The Wharton School, Philadelphia, and a Bachelor of Technology from IIT (Kanpur), India.

QUALITY CONTROL

Designing Quality Into the Manufacture of Adhesives Targeted for Healthcare Applications

By: Katherine L. Ulman, Irena Ziec, and David J. Neun, PhD

ABSTRACT

With additional regulatory and quality requirements for active and inactive pharmaceutical ingredients, it is increasingly important for suppliers to keep abreast of regulatory trends while partnering with pharmaceutical manufacturers to understand and meet their product needs. The Dow Corning and Rohm and Haas medical adhesives alliance has defined and implemented principles of "quality by design" into manufacturing and distribution operations for producing pressure-sensitive adhesives targeted for transdermal drug delivery systems and drug-loaded patches.

INTRODUCTION

Emerging regulatory trends for pharmaceutical products continue to focus on topics such as global harmonization, process analytical technology (PAT), good manufacturing practices (GMPs), quality by design, science-based regulations, and risk-based pharmaceutical assessments. These initiatives challenge healthcare manufacturers to build quality and safety into their products from initial development and design, through manufacture, launch, and post-launch surveillance. As a result, pharmaceutical manufacturers continue to place higher expectations for improved raw material quality and safety on their suppliers by asking them to help define and build the proper level of controls into their manufacturing and distribution operations.

Incorporating quality into the design of a product not only involves building in critical quality elements of GMPs (eg, traceability, change control, and notification of change and contamination control) and monitoring quality indicators from development throughout a product's life cycle, but also includes implementing elements of continuous improvement and risk management principles.

ESTABLISHING A ROBUST QUALITY SYSTEM

Although the ISO 9000 family of quality management standards has earned a worldwide reputation as a "generic management system" that delivers a valuable framework for quality, the standards focus mainly on the "what" rather than the "how" and on the end result rather than the entire manufacturing process. In today's environment, it is also essential to incorporate appropriate GMP principles into the production, handling, and distribution of pharmaceutical products. However, selecting the appropriate guidelines and level of GMPs to implement can pose a challenge for developers, raw material suppliers, and finished product manufacturers.[1-3]

To ensure the establishment of proper manufacturing controls for pressure-sensitive adhesives targeted for use in drug delivery systems, the Dow Corning and Rohm and Haas team agreed to manufacture the adhesives in facilities capable of implementing critical GMP principles. Criteria defined as critical by the team include a quality management system, management commitment to quality, quality training program(s), complete product traceability (throughout the entire supply chain), process/product/document control, contamination control, and change control aligned with customer notification of change.

RISK-BASED APPROACH TO CRITICAL GMP ACTIVITIES

Governmental regulations (laws, standards, and guidelines) are developed to ensure the continued production of products that are safe and effective for their intended use. In the US, these regulations include compliance to 21 CFR 210/211 for companies producing bulk pharmaceutical active ingredients and finished drug products. In addition, a GMP guidance specific to active pharmaceutical ingredients (ICH Q7A) has been drafted and accepted or adopted as law by many countries. In the US, ICH Q7A is currently accepted as a guidance document; however, inspectors often refer

to it when conducting GMP inspections of both bulk and finished pharmaceutical product operations.

Today, regulations do not specify quality and safety operations for excipients; however, guidance documents (from IPEC, PQG, WHO) identify critical GMP elements to consider. Additionally, excipient suppliers should understand the risk of what could go wrong, and if it went wrong, what impact it could have on product safety and efficacy. Effective use of risk management can facilitate better, more informed decisions and provide regulators with greater assurance of a company's ability to deal with potential issues.

Quality Management System & Management Commitment

To ensure product safety and efficacy, an excipient manufacturer should implement a quality management system that has the full support and commitment from the management team. The team's role and responsibilities should include periodic review of quality-related topics and issues, including complaints, audit findings, nonconforming products, and supplier issues.

Quality Training Program

A program dedicated to ensuring proper employee training, including quality system training in GMPs, is essential for everyone involved in producing, packaging, storing, and shipping pharmaceutical excipients. The training program should define how changes in regulatory requirements are monitored, interpreted, and communicated to employees and should include the following:

- **Management:** Properly trained management and staff are important to demonstrate management's commitment for GMP operations and compliance.

- **Operators:** Proper operator training is paramount as properly trained operators can play a significant role in helping to minimize contamination, improve process control, and make informed decisions about inconsistencies or abnormalities that could occur during the manufacturing process. Operators should also be trained in proper handling and labeling of the finished product.

- **Shipping/Receiving/Warehousing:** Shipping, receiving, and warehousing personnel are responsible for receiving, handling, storing, and transporting raw materials, intermediates, and finished products. Procedures must be in place to prevent mix-up and contamination of material during each of these operations.

- **Quality Assurance/Control:** The quality department is responsible for managing and controlling quality aspects of raw materials, intermediates, and finished product. For instance, raw material certificates of analysis (COAs) and identity checks are made to ensure the product is what it is supposed to be and meets lot acceptance criteria. Quality personnel review and approve changes (eg, equipment, process, raw materials, and test methods) prior to evaluation and implementation. They also review/approve batch records prior to product release to ensure complete and accurate records (eg, acceptable critical process parameters and final lot testing, required signatures, and required documentation).

Product Traceability Throughout the Entire Supply Chain

It is important to be able to trace the final product from raw material receipt through production of intermediates and finished products (eg, cleaning agents/operations, equipment identification, and detailed batch records), including people who handled it, equipment used to manufacture and/or test it, packaging components (eg, containers, labels, etc) used to package it, and the handling and storage conditions used to warehouse and ship it. To ensure good traceability, containers should be clearly labeled to identify the contents. Materials not required for operations should be removed from the production area, including removal and destruction of excess labels.

These measures help ensure full traceability of product, manufacturing, testing, packaging, storage, and distribution operations, which can simplify root cause analysis of noncomplying product, help identify other potentially impacted batches, and help provide assurance for nonaffected batches.

Process/Product/Document Control

To meet emerging requirements, excipient manufacturers need to monitor, understand, and control their raw materials, intermediates, and finished products throughout their entire supply chain (from receipt of materials through delivery to pharmaceutical manufacturing facilities).

PROCESS CONTROL

It is important to understand and plan for quality (ie, to control and manage variability) at the design phase versus testing for compliance at the end. A good process design should include understanding the impact on quality and performance when certain parameters are varied. By striving for better process understanding and capability analysis, excipient suppliers should be able to design quality in and facilitate risk-based decisions for continuous improvements. Validation and change control should be considered to ensure process control.

PRODUCT CONTROL

In addition to controlling the process, the product needs to be monitored and controlled throughout its life cycle. Good product control includes such factors as:

- Contamination control to verify adequacy of cross-contamination prevention, sanitary conditions, ventilation, lighting, cleaning agents/program, etc.
- Nonconforming product control, whereby a separate area is designated and controlled for materials that do not meet requirements.
- Corrective and preventive actions (reprocessing/rework disposition, rework authorization, corrective/preventative action plans, and progress reviews).
- Sample retention, in which twice the amount of sample required to perform all specification testing is kept for each batch for at least 1 year past the expiration date, re-evaluation date, or after distribution is complete (whichever is longer).
- Defined stability testing criteria and protocols.
- Out of specifications (OOS) procedure consistent with FDA guidance.[4]

DOCUMENT CONTROL

Document control should include control of all quality system documentation, including the quality manual, procedures, and records (eg, master product files; batch records; labels; and quality department review, approval, release). Each batch production record should include process SOPs and pertinent product information, such as raw material/quantity, packaging material(s), labeling, label reconciliation, equipment used, and operators. Batch records should be reviewed and approved by QA personnel prior to product release.

Contamination Control

Although no specific guideline or regulation requires the identification and control of impurities in excipients, this factor should be considered as critical during the manufacture of pharmaceutical excipients, and several API guidelines can be referenced (ICH Q3C), USP NF <467> , and Ph Eur. general chapter 5.4.[5-7] Even manufacturing an excipient in a closed system can lead to product contamination; therefore, contamination control should include a review of building and facilities design, materials flow, and storage, cleaning agents and operations, lubricants, environmental monitoring/control, and pest control, as well as manufacturing, testing, packaging, and storage operations.

At GMP manufacturing sites, procedures are developed, documented, and implemented to minimize potential sources of contamination, including:

- **Lubricants:** Use of appropriate grade (eg, food grade).
- **Pest Control:** Based on an understanding of the process (eg, open vs. closed system), appropriate measures are taken to minimize potential contamination from insect, birds/bird droppings, rodents, and similar contaminants.
- **Cleaning Process:** Cleaning agent selection includes a review for potential toxicity. When possible, a final rinse is made with solvent used in the product. The complexity and thoroughness of the cleaning process is determined based on knowledge of other materials manufactured in the same equipment and can be simplified by campaigning similar products.
- **Material Handling:** When possible, bulk materials are used and direct operator handling is minimized. Personal protective equipment is used to minimize contaminations when appropriate.

Change Control Aligned With Customer Notification of Change

In the early stages of product development, a formulator selects adhesive products that aid in delivering the drug substance as desired. Once the formula and process have been defined and optimized, the impact of adhesive variability (batch-to-batch) is determined, and final scale-up to pilot and production equipment is completed. At this point, it is critical for subsequent batches to be within established specification limits and equivalent (quality and performance) to initial batch(es) evaluated.

Changes are inevitable; however, managing and controlling change is critical to ensuring consistent product quality and safety. Even changes that may seem minor (eg, raw material suppliers, change in cleaning agents, new test procedures or equipment, or changes in manufacturing location) should be properly evaluated for their impact on the final quality and performance of the products being produced. In addition, customers should be properly notified of any change that could potentially impact the quality, safety, or performance of a product.

ATTENTION TO EMERGING REGULATORY TRENDS

As a result of global initiatives, pharmaceutical manufacturing is currently transitioning from an art to a science, and excipient suppliers increasingly are being asked to design quality into their products. Regulatory standards and policies are being designed to ensure continued quality, safety, and efficacy of pharmaceutical products, including excipients. In addition, the scientific framework being developed will help support mitigation of risk while facilitating continuous improvement and innovation. Current trends include the following:

- US FDA cGMPs for the 21st century;
- Controlling product source (eg, BSE);
- Guidelines for residual solvents and/or impurities in drug products: ICH Q3C, USP NF <467>, Ph Eur. general chapter 5.4;[5-7]
- ICH Guidance on Pharmaceutical Development, ICH Q8, and draft guidance on Quality Risk Management Process, ICH Q9;[8,9] and
- US FDA guidance on Non-clinical Studies for the Safety Evaluation of Pharmaceutical Excipients.[10]

SUMMARY

Based on emerging global trends, the process of controlling the quality and consistency of excipients while ensuring they are well characterized, robust, and meet regulatory requirements is a critical expectation for excipient suppliers.[11] Currently, the pharmaceutical industry's average timeframe for development and regulatory approval of a new TDD system can be upward of 7 years for new drugs and about 5 years for generic drugs; however, there are steps that raw material suppliers can take to help facilitate and reduce these time lines:[12,13]

- Provide adhesives (based on established adhesive technology) that can be easily adjusted or customized to meet the needs of various transdermal systems (eg, adhesive properties, solubility parameters, stability, and aesthetics).
- Form partnerships with pharmaceutical manufacturers to support their needs throughout the life cycle of their products (eg, development, clinical trials, scale-up and validation, launch, and continued supply).
- Ensure a healthy quality system staffed by necessary experts (engineers and laboratory personnel) and designed to effectively manage (identify, assess, and internally and externally communicate) change throughout the life cycle of a product.
- Utilize toxicology studies, global regulatory resources, and documentation [eg, drug master files (DMFs) or letters of access (LOAs)] to support product registration and approval around the world.
- Produce adhesives in GMP facilities using critical GMP principles of traceability, process/product control, contamination control, documentation/records, training, and change control/communication of change.

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BIOGRAPHIES

Ms. Katherine Ulman is the Global Technology Coordinator for Dow Corning Healthcare Industries and is the Technical Coordinator at Dow Corning for the healthcare alliance between Dow Corning and Rohm and Haas. Prior to this position, she was the Regulatory Manager for the Dow Corning Healthcare Industries. Ms. Ulman is a member of the American Chemical Society, American Association of Pharmaceutical Scientists, Control Release Society, and the IPEC of the Americas. She has published and presented several papers in her field and has taught international courses on silicones for pharmaceutical/ biomedical applications and medical adhesives through Technomic Publishing Co. Ms. Ulman earned her BSc in Chemistry from the South Dakota School of Mines and Technology in 1976.

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Dr. David J. Neun is the Global Regulatory Steward for Healthcare Industries of Dow Corning Corporation responsible for regulatory affairs and product stewardship. He is a Toxicologist with over 10 years experience with ingredients for the healthcare market. Prior to joining Dow Corning Corporation, Dr. Neun was the Research Director for the Soap and Detergent Association in the United States, responsible for assessing alternative tests to the use of animals and risk assessment for detergent products and their ingredients.

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Understanding Competition

By: John A. Bermingham

John A. Bermingham joined Ampad as President and CEO in August 2003 when Ampad was acquired by group of investors composed of an affiliate of Crescent Capital Investments, himself, and another private investor. He also serves as Chairman of the company's Board of Directors. Previously at the helm of numerous industry-leading companies, Mr. Bermingham brings more than 20 years' experience in guiding enterprises to new levels of performance. Most recently prior to joining Ampad, Mr. Bermingham held the positions of Chairman, President, and CEO of Centis, Inc., a diverse multinational manufacturer and marketer of office, storage, and human resources products. Prior to joining Centis, Mr. Bermingham successfully leveraged the potentials of two start-up companies, raising capital, forging key relationships, and establishing the structure and direction that would pave the way for future growth and achievement. Among his many career highlights in the role of President and CEO for companies serving the office products industry, Mr. Bermingham successfully reorganized Smith Corona Corporation, restoring the company's stability, profitability, and reputation. At Rolodex Corporation, he refocused operations and a strategic vision for a dramatic turnaround in corporate culture, and phenomenal increases in both revenue growth and cashflow. Mr. Bermingham's expertise in leveraging technology and optimizing resources for the business products/services markets has also been deployed at industry giants, such as AT&T Consumer Products Group, and by having served as the EVP of the Electronics Group and President of the Magnetic Products Group, Sony Corporation of America. Mr. Bermingham served three years in the U.S. Army Signal Corps with responsibility for Top Secret Cryptographic Codes and Top Secret Nuclear Release Codes. Earning a BA in Business Administration from Saint Leo University in Florida, Mr. Bermingham has also completed the Harvard University Graduate School of Business Advanced Management Program.

A few issues ago, our Executive Editorial Director, Dan Marino, asked me to write a column on understanding competition. If you don't mind Dan-O, I would like to put a little spin on that request.It was so bad that we named his alter ego Frank. Fred was good. Frank was bad.

It is always important not just to know what's happening with your competition but to also *really understand* your competition. The obvious methods, amongst many, are to conduct marketing research, read trade journals, and review press releases. You should also talk with your customers to see what you can find out about competition, but sometimes that can be a little dicey.

When I talk about understanding your competition, I am talking about understanding how your competition does things; how they react to competitive offerings or promotions; how fast they are in reacting overall; how aggressive they are on pricing; and how marketing driven they are. More so, I am a believer in understanding the actual people you are competing with. What are their personalities and how do they personally react to competitive offerings or promotions?

When I was a National Sales Manager for a company in my earlier days, we had a competitor that was led by a person who was completely irrational. Whenever we came out with a new sales promotion, this person would bounce off walls and berate his sales and marketing people for letting us get the jump on them. An excellent tactic with sales and marketing people!

So when we would look to take market share from this competitor, we would go right at them with sales promotions that were value-added promotions rather than price oriented. We knew they would quickly meet a price-oriented promotion but had trouble reacting to a value-added one. (If you are not familiar with this, value added means to buy something and get something else for free). Other competitors had management that would react in different ways, so we always kept that in mind when developing programs and product offerings.

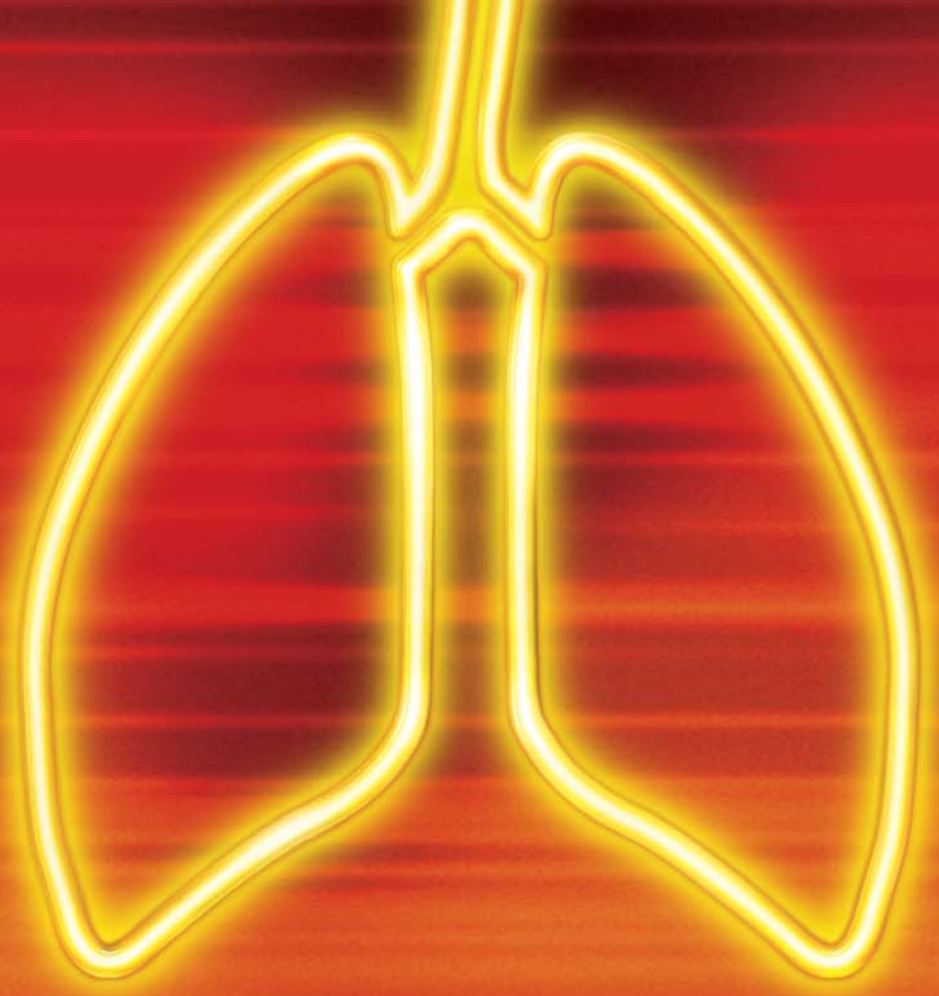
Now for the spin. Do you know that you are the best source of competitive information on your company for your competitors. True! I can't tell you how many times I have listened to someone in a restaurant, airport, particularly on an airplane, or in other venues talk about their company as if no one else is around. I especially enjoy hearing two or more people talk very negatively about their company and/or management. I also enjoy listening to people talk on their cell phones about their company or management to others.

Many years ago, I learned this lesson about you being the best source of competition information on your company. While flying back to Newark from the Consumer Electronics Show in Las Vegas, I sat right behind the National Sales Manager and the National Marketing Manager of my largest competitor. Throughout that flight, they reviewed everything a competitor would want to know about their company strategy for the coming year. It was amazing! I sat there with a note pad and wrote down everything they said.

A few months ago, I was flying from Dallas back to Newark and sat next to a person from Avon Products. This person was on her cell phone prior to the door being closed and, in a loud voice, reviewed the company's pricing strategy to include reviewing a long list of their costs, product by product. Everyone within 10 rows could hear everything she said. I couldn't believe it!

I continually coach our people on talking about the company in any public venue. Especially airports and aircraft, either directly to others or via cell phones. Restaurants follow closely behind. Those that concern me most are sales, marketing, product, and R&D people. These people have vast amounts of information that competition would love to have. So I coach and remind them the most. So we all have to think about this problem constantly and always be aware that you never know who is sitting around you.

Listen carefully the next time you are in a public venue to the people talking around you. You will be amazed how much confidential information they relate to others on their company. ♦



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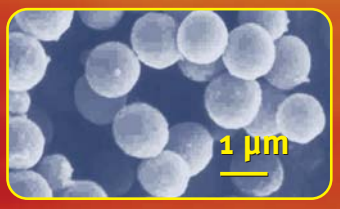

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