Drug Delivery Technology®

March 2006 Vol 6 No 3

The State of Non-Invasive Insulin Therapy

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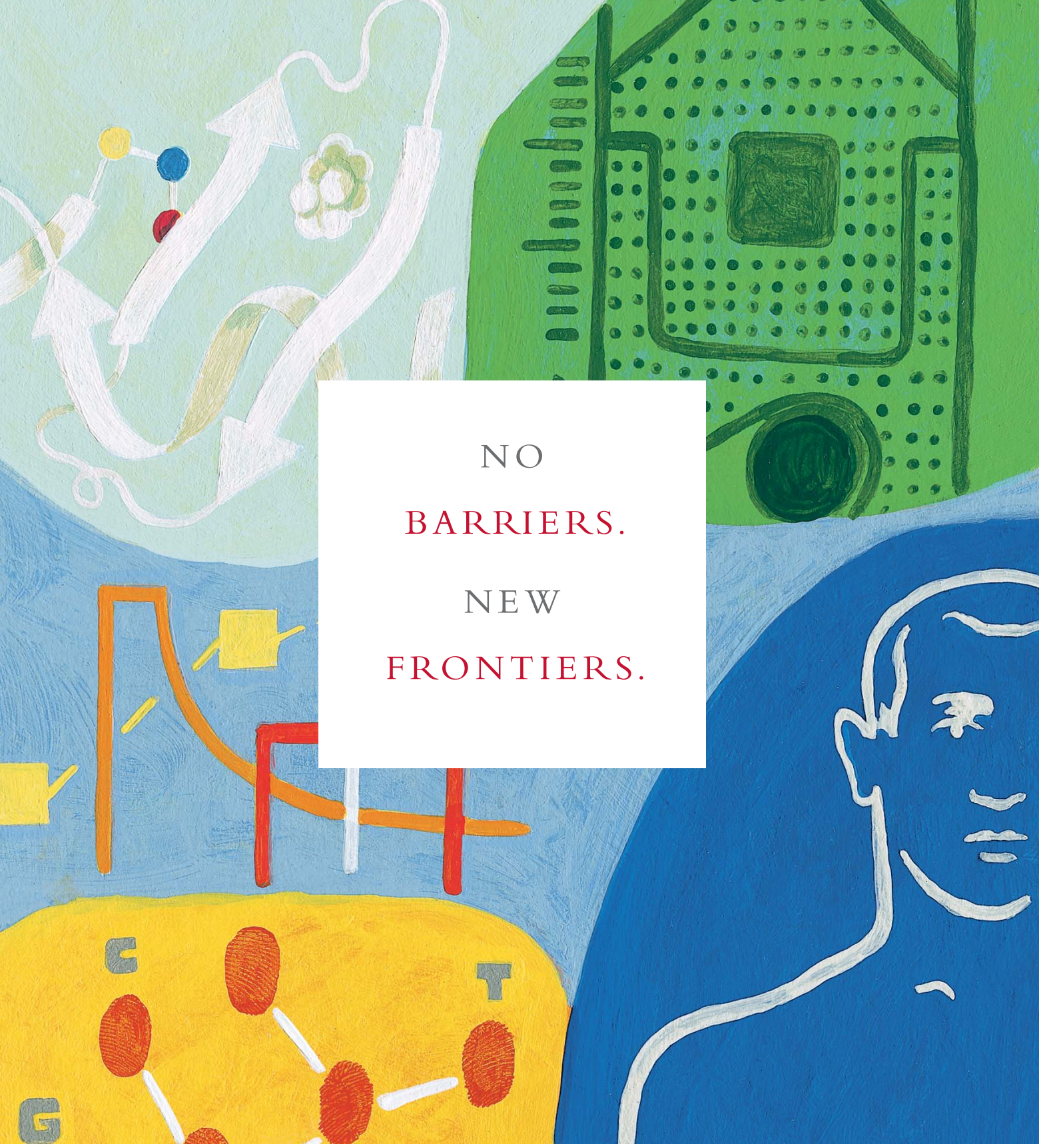

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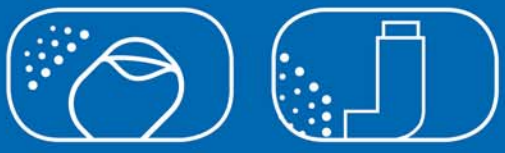

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[i] Wiess, P.M., http://www.femalepatient.com/html/arc/sig/pharma/articles/028_07_031.asp
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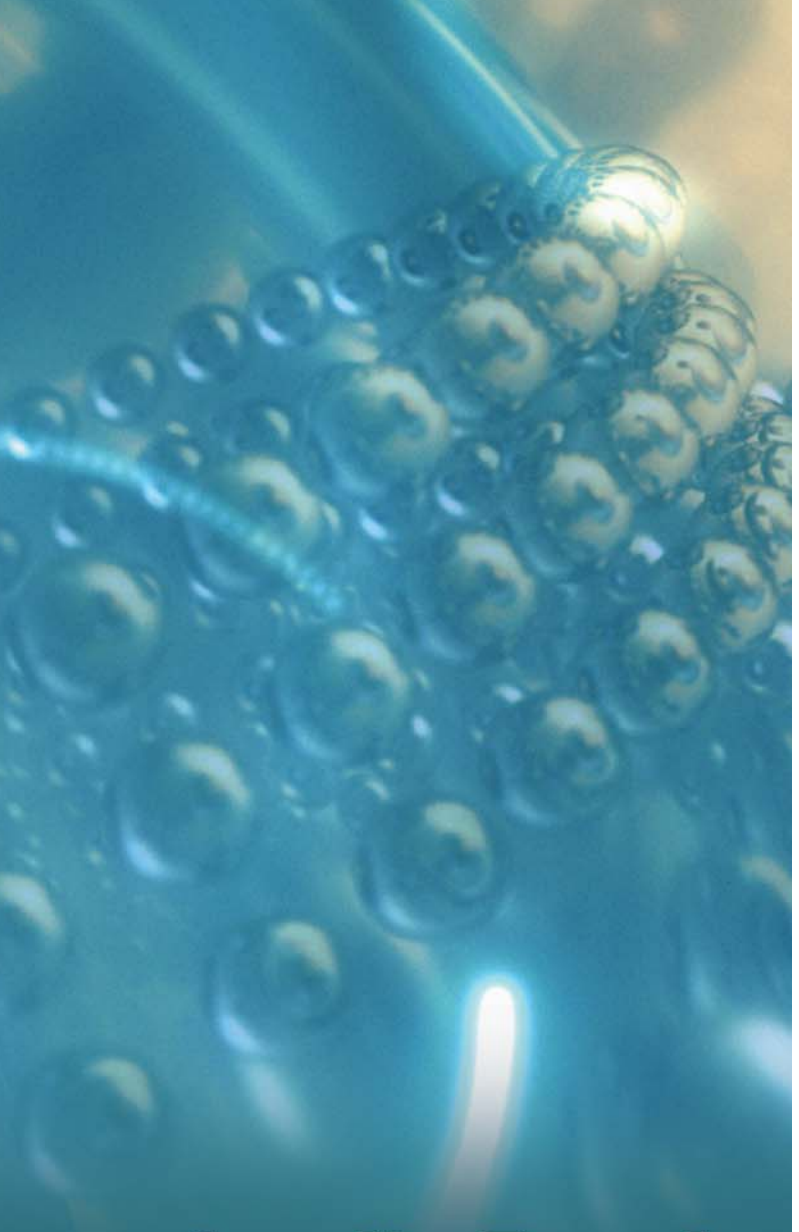

Insulin Trends & Prospects

"This new millennium promises a revolutionary change in the delivery of insulin, which is not too far off for billions of sufferers who are reliant on subcutaneous administration."

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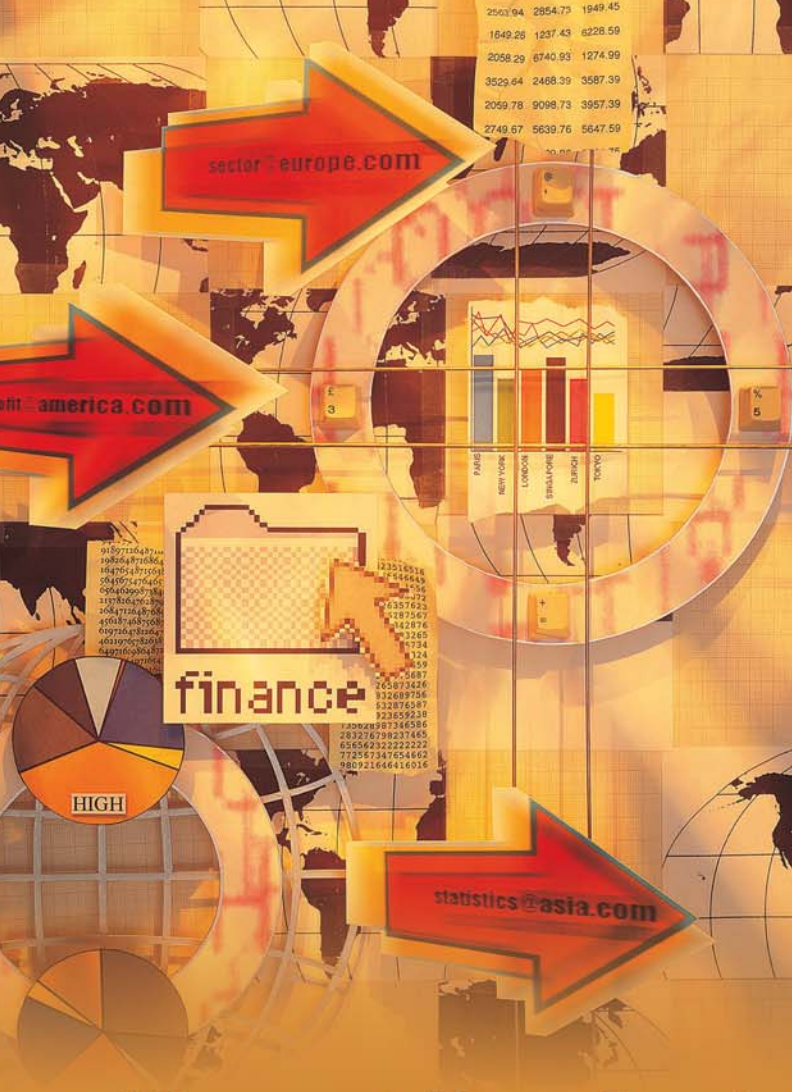

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Recent Product Deal Terms

"The deal terms for the best of these transactions are close to terms offered for biotechnology products at comparable stages of development. To get to these valuations, the Drug Delivery products do not simply enhance the performance of the active; rather they define a whole new therapeutic solution."

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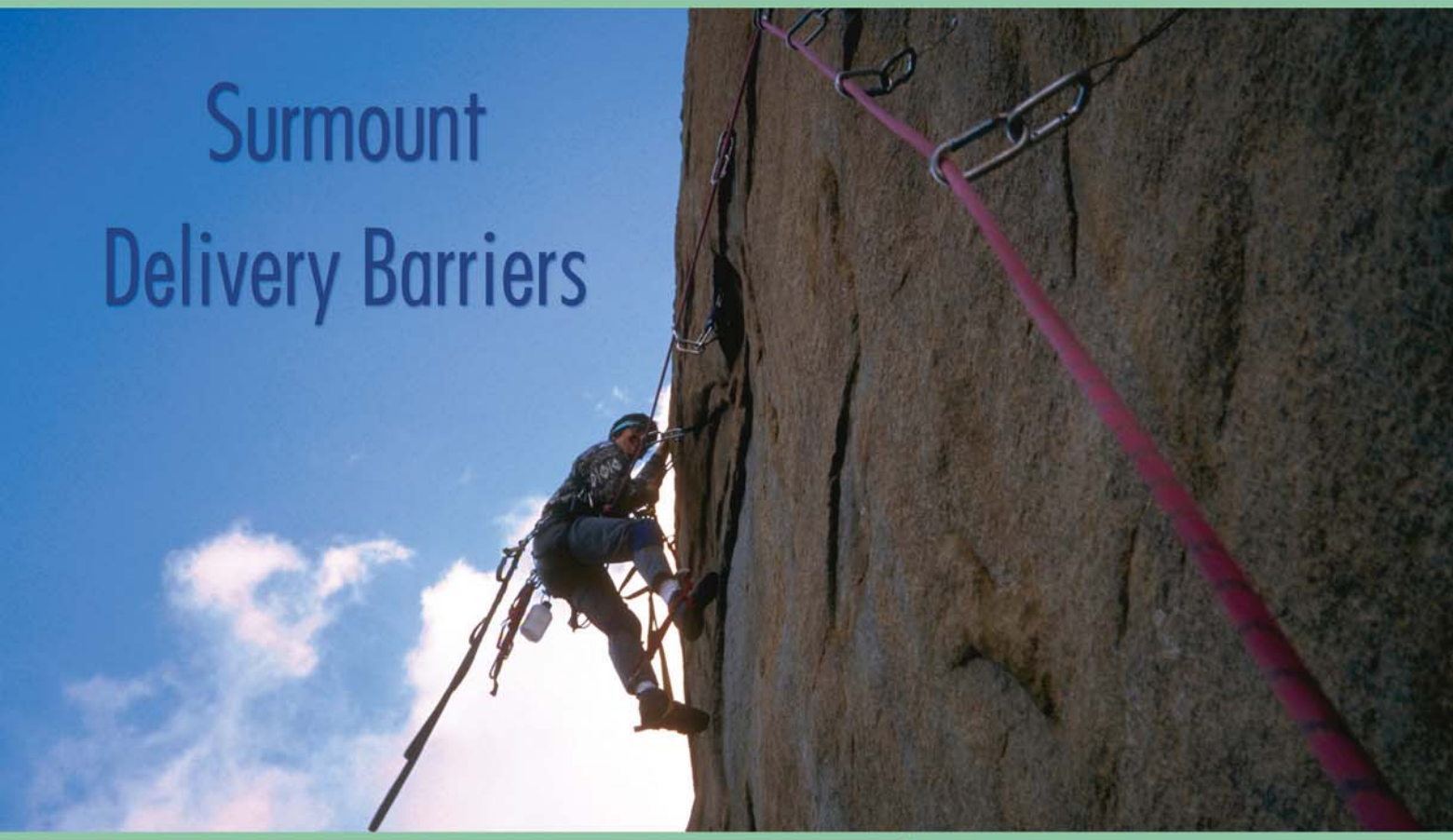
In Every Issue



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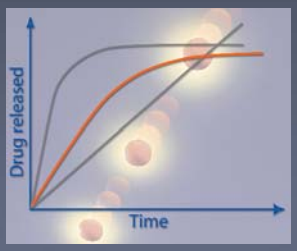

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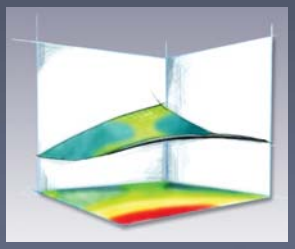
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MARKET NEWS and TRENDS

Viventia Biotech & Dowpharma Announce Multi-Product Commercial License Agreement Using Pfenex Expression Technology™

Viventia Biotech, Inc., and ***Dowpharma*** contract manufacturing services, a business unit of The Dow Chemical Company recently announced they have entered into a commercial license agreement for Pfenex Expression Technology™, a Pseudomonas-based technology from Dowpharma.

Under the terms of the agreement, Viventia will employ Pfenex Expression Technology for up to six different therapeutic compounds, the first of which is an antibody-based product candidate in preclinical development. Pfenex Expression Technology accelerates speed to market for vaccines and biotherapeutics by improving quality, boosting yields of difficult-to-express proteins, and reducing the cost of existing microbial systems. The agreement specifies milestone payments and commercial royalties on product sales; additional financial details were not disclosed.

"Our proprietary Armed Antibodies™ platform is a cutting-edge approach yielding powerful yet precise antibody-based therapeutics for the treatment of a variety of cancers," said Nick Glover, PhD, Chief Executive Officer of Viventia Biotech. "To support the commercialization strategies for our drugs, it is essential that we be able to produce our Armed Antibodies efficiently and at commercially viable levels. Pfenex may enable us to increase the expression of our Armed Antibodies beyond the levels of other expression technologies and speed our process development."

"We look forward to expanding the technology applicability of Pfenex by expressing antibody-based products, which are traditionally very difficult to express," said Nick Hyde, Global Business Director, Dowpharma. "This agreement further validates the biopharmaceutical industry's need to more quickly and efficiently produce biotherapeutics."

Dowpharma has an unmatched record in developing high-productivity strains for the manufacture of numerous protein products for both clinical and industrial applications. Pfenex Expression Technology is built around specially modified strains of Pseudomonas fluorescens bacteria that increase cellular expression of recombinant proteins and peptides while maintaining critical solubility and activity characteristics. Pfenex Expression Technology consistently outperforms other microbial systems, often with yields 5 to 10 times greater than the next best expression alternative.

Dowpharma serves the pharmaceutical and biopharmaceutical industries with innovative technologies, products, and services in drug discovery, development, delivery, and manufacturing. Dowpharma has one of the broadest and deepest capabilities in the global outsourcing industry with services that include process development, route selection, methods development, custom solubilization, chiral capabilities, and associated analytical services, as well as manufacturing and scale-up from feasibility, through clinical trials, to commercial manufacturing. Dowpharma manufactures small molecule Active Pharmaceutical Ingredients (APIs) and intermediates, nucleic acid medicines, cGMP polymers, peptides, and therapeutic proteins from microbial fermentation and plant-based systems.

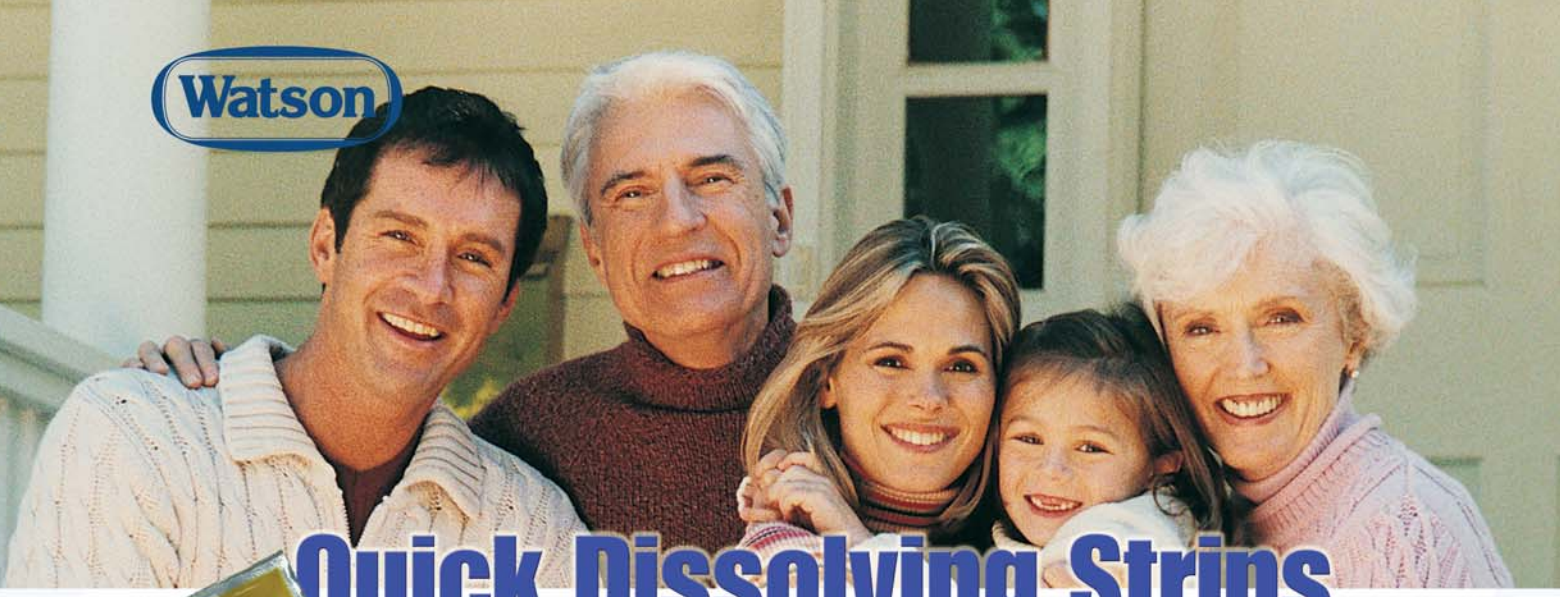
Viventia Biotech, Inc., is a biopharmaceutical company developing Armed Antibodies powerful and precise anti-cancer drugs designed to overcome various forms of cancer. Viventia's lead products, Proxinium™ and Vicinium™, combine a cytotoxic protein payload significantly more powerful than traditional chemotherapies with the highly precise tumor-targeting characteristics of a monoclonal antibody. Proxinium and Vicinium are in clinical development for the treatment of head and neck cancer and bladder cancer, respectively.

Emisphere Technologies Achieves Second Milestone in Roche Collaboration; Payments Could Total $37 Million

Emisphere Technologies, Inc., recently announced it has achieved a second milestone under its November 2004 agreement with Roche to develop new oral formulations of a Roche small molecule compound for the treatment of bone-related diseases. The achievement of this milestone, resulting in an undisclosed payment from Roche, arises from Roche's initiation of a clinical study utilizing Emisphere's eligen® delivery technology in a formulation for a second product. Emisphere previously received a milestone payment for developments relating to a different product and indication announced in July 2005. With two products now being developed by Roche using the eligen technology, milestone payments could total $37 million.

Roche is utilizing Emisphere's eligen technology to evaluate new formulations that may be more convenient for patients than the formulation of products currently on the market. Under the terms of the original agreement, Roche paid Emisphere an initial up-front fee, and agreed that Emisphere may receive up to $18.5 million in milestone payments for each product developed using the eligen technology. Emisphere may receive royalties based upon product sales for this product and for the first product. Roche will fund all necessary preclinical, clinical, and manufacturing costs for all products.

"Achieving this second milestone further underscores the broad applicability of our oral drug delivery technology and its attractiveness to our pharmaceutical partners," said Michael M. Goldberg, MD, Chairman and Chief Executive Officer, Emisphere. "We are pleased that Roche has chosen to work with Emisphere to gain access to our proprietary carriers, and believe there is near-term commercial value in our oral delivery technology for more than one product."



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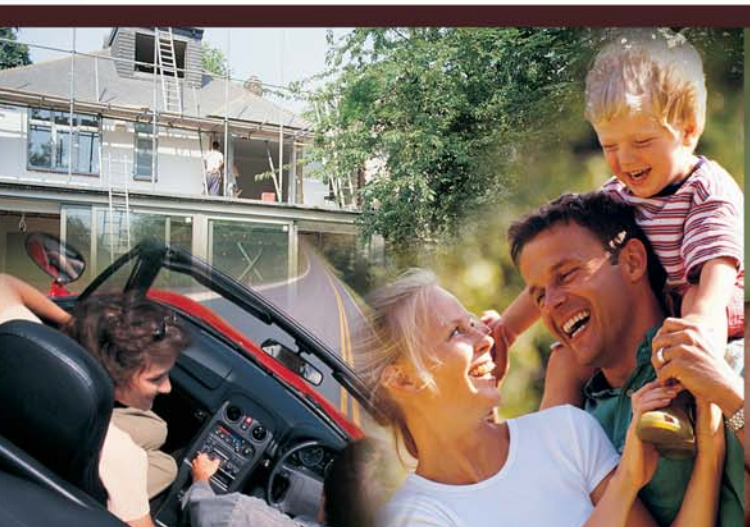


Stealthyx Therapeutics & Cancer Research Technology Announce Co-Development Partnership for Tumor-Targeted Therapy

Cancer Research Technology (CRT), the specialist oncology development and commercialization company, and Stealthyx Therapeutics, the disease-targeting drug company spin out of Queen Mary, University of London have entered into an agreement to co-develop Stealthyx's proprietary drug delivery platform, Prothyx™. The Prothyx platform adds extra functionality to therapeutic molecules, making them preferentially active at sites of disease. Localizing a drug's activity only to the diseased tissue promises to minimize adverse side effects on other tissues and may enable higher doses of drugs to be given less frequently.

Under the terms of the agreement, CRT has obtained worldwide exclusive rights to develop and commercialize the Prothyx platform within the field of oncology and will perform in-house development of candidate Prothyx-based anti-cancer therapies. Stealthyx will exploit developments arising from the program in other therapeutic areas, including rheumatoid arthritis.

"In-licensing of promising technologies from commercial parties to accelerate the development of novel cancer therapies highlights our continued commitment to the realization of cancer patient benefit," said Phil L'Huillier, Director of Business Management at CRT.

"CRT's co-development support for Prothyx endorses the important potential of our technology in cancer, where there are great opportunities to improve patients' clinical outcomes, and minimize the distressing side effects of some cancer treatments," added Professor Yuti Chernajovsky, Founder of Stealthyx Therapeutics and ARC Chair of Rheumatology at Queen Mary, University of London. "I look forward to working with our partners to help bring safer medicines to the market."

Cancer Research Technology Limited is a specialist commercialization and development company, which aims to develop new discoveries in cancer research for the benefit of cancer patients. CRT works closely with leading international cancer scientists and their institutes to protect intellectual property arising from their research and to establish links with commercial partners. CRT facilitates the discovery, development, and marketing of new cancer therapeutics, vaccines, diagnostics, and enabling technologies. CRT is wholly owned by Cancer Research UK, the largest independent funder of cancer research in the world.

Stealthyx Therapeutics Limited was founded in 2002 to commercialize the novel Prothyx technology platform that was discovered by Prof Yuti Chernajovsky at Queen Mary, University of London. Stealthyx Therapeutics has received seed funding from Kinetique Biomedical Seed Fund, and a Wellcome Trust Translational award to develop the technology to the proof of concept stage.

MARKET NEWS and TRENDS

BD's Micro-Delivery System Licensed by Sanofi Pasteur; Hypak™ Platform Used by GlaxoSmithKline for Recently Launched Prefilled Flu Vaccine

BD (Becton, Dickinson and Company) recently has entered into an agreement with sanofi pasteur, the vaccines business of the sanofi-aventis Group to license the BD Micro-Delivery System for use in the administration of sanofi pasteur's human vaccine products.

Most vaccines are delivered via intramuscular injection. This BD patented technology provides a new method of delivering vaccine into the upper layer of the skin. The results of early-phase clinical research have shown that this method of delivery has the potential to improve the immunogenicity and efficiency of the delivered vaccine.

"We are very pleased to enter into this collaboration with sanofi pasteur," said Gary Cohen, President, BD Medical. "We believe that our BD Micro-Delivery System has the potential to help address some of the important health challenges facing the world today, and embodies BD's company purpose of helping all people live healthy lives."

The BD Micro-Delivery System is designed to be prefilled with vaccine and to easily and reliably deliver the vaccine to the skin. The system features a tiny "microneedle." Clinical testing indicates that the "microneedle" is barely perceptible when it enters the skin.

"In practical terms, the BD Micro-Delivery System has the potential to increase a patient's acceptance of vaccine as well and enable vaccination of more people with less vaccine," said Alexandre Conroy, President, BD Medical - Pharmaceutical Systems.

Under the terms of the agreement, BD will provide sanofi pasteur with a license to the BD Micro-Delivery System in the field of human vaccines. The parties will continue to work together to demonstrate its applicability to delivering a wide variety of vaccines, including the influenza vaccine that is now being tested in human clinical trials conducted in conjunction with the US National Institutes of Allergy and Infectious Diseases. Per the agreement, BD will be compensated for use of the BD Micro-Delivery System provided to sanofi pasteur, which will develop, manufacture, and commercialize the vaccine-filled BD Micro-Delivery Systems.

BD Medical, a segment of BD, also recently announced that GlaxoSmithKline (GSK) is using the BD Hypak SCF™ prefillable syringe system for their recently approved prefilled flu vaccine offering available in the US.

"We were proud to be associated with GSK on this effort, and we congratulate them on the FDA approval of their prefilled flu vaccine offering," said Linda Tharby, Vice President and General Manager US, BD Medical – Pharmaceutical Systems. "For more than half a century, the BD Hypak prefill platform has been at the forefront in helping to provide our pharmaceutical partners real solutions in optimizing vaccine supply to meet the growing public need for vaccines and innovative solutions for some of the world's leading public health concerns."

BD Hypak prefill's newest innovation, the BD Hypak PRTC glass prefillable syringe, will be used by GSK for their new prefilled flu vaccine offering. It is the first prefilled flu vaccine for people aged 18 to 64 offered exclusively in prefilled syringes, which GSK markets under the brand name Tip-Lok®.

The BD Hypak PRTC prefilled syringe technology features a specially designed plastic tip cap with familiar twist-off mechanism preferred by healthcare professionals. Additionally, BD Hypak prefills require minimal overfill over the desired dose and minimize medication errors; as a result, they contribute reductions in the cost of care and drug deliveries.

Features of this latest BD Hypak SCF advancement include innovative tip cap design that facilitates aseptic technique during tip cap removal, securely attached tip cap for optimum integrity of syringe tip and contents, easy and convenient-to-open tip cap, and transparent BD Luer-Lok™ adaptor for visual inspection of the needle hub connection compatible with conventional and safety-engineered needles.

In the US, BD Hypak SCF is the medication delivery system selected and used for prefilled flu vaccine and remains the preferred medication delivery system by pharmaceutical companies for vaccines and therapeutic drugs.

BD, a leading global medical technology company that makes and sells medical devices, instrumented systems, and reagents, is dedicated to improving people's health throughout the world. BD is focused on improving drug therapy, enhancing the quality and speed of diagnosing infectious diseases, and advancing research and discovery of new drugs and vaccines. The company's capabilities are instrumental in combating many of the world's most pressing diseases. Founded in 1897 and headquartered in Franklin Lakes, New Jersey, BD employs more than 25,000 people in approximately 50 countries throughout the world.

MARKET NEWS and TRENDS

Altea Therapeutics & Teikoku Seiyaku Announce Agreement to Develop, Manufacture & Commercialize in Japan New Transdermal Therapy for Parkinson's Disease

Altea Therapeutics recently announced it has entered an exclusive licensing agreement for Japan with Teikoku Seiyaku Co. Ltd. to develop and commercialize a new transdermal patch therapy that utilizes the Altea Therapeutics PassPort™ transdermal technology to deliver an active pharmaceutical ingredient for managing Parkinson's Disease.

Under the terms of the agreement, Teikoku Seiyaku will pay Altea Therapeutics a signing fee and additional payments upon completion of certain development milestones. Teikoku Seiyaku will pay undisclosed royalties on net sales and/or net revenues and also fund the cost of Japanese product development. Additionally, Teikoku Seiyaku has an option to negotiate terms for exclusive Japanese market rights for certain additional products based on the PassPort System.

"This is a first in what is expected to be a number of collaborations based on our proprietary PassPort System technology that enables painless, efficient transdermal delivery of sustained therapeutic levels of proteins and water-soluble molecules from a skin patch", stated Eric Tomlinson, President and Chief Executive Officer of Altea Therapeutics. "We are delighted to have Teikoku Seiyaku as our first product development, manufacturing, and commercialization partner. We look forward to a long and mutually successful relationship as we work together to develop important new and innovative therapies for the Japanese market."

Altea Therapeutics is an emerging private pharmaceutical company focused on developing and commercializing a broad portfolio of pharmaceutical products based on a new class of advanced transdermal patches that deliver sustained therapeutic levels of proteins and highly water-soluble drugs in a convenient, painless, and cost-effective manner. The company has demonstrated in several clinical studies that its patented PassPort transdermal system achieves what existing patches are unable to do, namely the continuous delivery through the skin of proteins and highly water-soluble drugs, compounds typically administered by painful needle injections. It has completed initial Phase II clinical trials in the US with a daily hydromorphone patch for the rapid management of moderate-to-severe pain, and is conducting Phase I clinical trials in the US with insulin patches that provide continuous delivery of basal levels of insulin for people with diabetes.

Teikoku Seiyaku Co., Ltd. headquartered in Sanbonmatsu, Higashikagawa, Kagawa, Japan, is a world leader in manufacturing of medicated patches and a pioneer in the field of anti-inflammatory and analgesic plasters. Lidoderm®, Lidocaine Patches sold in the US are developed and manufactured by Teikoku Seiyaku. Teikoku Seiyaku is mainly proceeding in two directions. One is the products based on its innovative TTS technology. The other is the products for pain-relief.

DSM & IEP Sign Agreement to Screen & Develop Biocatalysts for Production of Pharmaceutical Intermediates

DSM Pharma Chemicals (DPC) recently announced it has entered into an R&D agreement with the German company IEP to discover and develop biocatalytic solutions designed to simplify and lower the cost of a variety of chemical transformations. Under the terms of the agreement, DSM Pharma Chemicals will identify the targeted chemical conversions, and IEP will screen for the appropriate biocatalyst. Subsequently, DSM Pharma Chemicals will scale-up these processes to manufacture pharmaceutical intermediates and active ingredients. IEP will receive research and development payments and be entitled to milestones and royalties on products commercialized by DSM Pharma Chemicals.

This partnership will combine the strength of DSM as supplier of pharmaceutical intermediates and active ingredients with the strengths of IEP in alcohol dehydrogenase technology. Biocatalysis has increasingly become the technology of choice to introduce chirality in fine-chemical processes. The use of biocatalysts often leads to less complex syntheses, lower production costs, and more sustainable production processes. DSM is the market leader in applied biocatalysis for fine-chemical applications and to date has developed more than 25 industrial-scale production processes using enzymatic catalysis. IEP has proprietary technology for discovering and optimizing alcohol dehydrogenases for the production of chiral alchohols.

"The technology of IEP complements our own capabilities in the synthetic use of biocatalysts, with current leadership positions in enzymes belonging to the hydrolase and lyase classes, by significantly strengthening our position in oxidoreductases" said Marcel Wubbolts, Competence Manager Biocatalysis & Biotransformations at DSM. "In our collaboration, we will be able to profit from the enzyme technology of IEP GmbH and the process scale experience in biocatalyst fermentation and application present at DSM. As a result of our collaboration, we expect to vastly expand the range of (chiral) alcohols that we can manufacture at commercial scale."

"Biocatalysis is clearly one of our core technologies in chemical custom manufacturing," added Dr. Ronald Gebhard, R&D Director of DSM Pharma Chemicals. "And they are one of the smart solutions that we can offer to the benefit of our customers."

"I am glad to see our bioreduction technology being used at DSM, adding synergistically to the vast capabilities and industrial expertise, which DSM already has in other enzyme classes and biocatalysis in general", said Ortwin Ertl, Founder and CEO of IEP. "Here at IEP, we work to invent bioreduction processes for our valued customers, which are very easy to scale and to operate."

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

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

The trial will involve approximately 20 clinical study sites in the US. Patient enrollment has commenced and is expected to be complete by end of June 2006. Results of the study are expected in the fourth quarter of 2006. The trial is designed to determine the safety and tolerability of EUR-1008M and will compare the active drug to placebo in improving absorption of fat and other nutrients. The protocol for the trial has been prepared in collaboration with the Cystic Fibrosis Foundation Therapeutic Development Network Coordinating Center.

EUR-1008M is a new and proprietary PEP developed by Eurand. It has been developed as a delayed-release capsule intended to provide consistent product dosing over time, and EUR-1008M will be available in multiple dosage strengths to provide flexibility and convenience in dosing.

"The commencement of these trials is a major milestone in our development of a new PEP formulation for the treatment of pancreatic insufficiency," said Gearóid Faherty, Chief Executive Officer of Eurand. "This new product builds on our 15 years of experience in developing and manufacturing pancreatic enzyme products, and we believe that if these Phase III trials are successful, EUR-1008M could represent a significant advance in the treatment of pancreatic insufficiency."

An additional trial of EUR-1008M in a pediatric population is expected to commence in the second quarter of 2006. The Phase III trial will be conducted in CF care centers in the US. The study will be a multi-center, double-blind, placebo-controlled, cross-over trial in patients over 7 years of age with pancreatic insufficiency and cystic fibrosis. The study will evaluate the safety and efficacy of EUR-1008M compared to placebo in improving coefficient of fat absorption, while assessing among other endpoints, improvements in protein and other nutrient absorption.

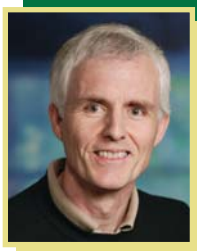
EUR-1008M is a new orally delivered pancreatic enzyme product consisting of approximately 14 enzymes, coenzymes, and cofactors. It is biologically similar to endogenous human pancreatic secretions and is intended to treat malabsorption of fats, proteins, carbohydrates, and other essential nutrients in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

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

Benchmarking Drug Delivery – Updated Product Terms

By: Josef Bossart, PhD

BIOGRAPHY



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

It's has been some time since we looked at the terms for product deals involving Drug Delivery products *(Benchmarking Drug Delivery – Product Terms, Drug Delivery Technology – September 2004)*. A surprising number of deals have been concluded in the interim that are starting to provide an idea of the range of reasonable terms for these transactions. These products are interesting in that unlike the products profiled in the 2004 article, these are not only "fallen angels," products that fell out of a technology collaboration or very early product deals with other companies. Several of these products were conceived and developed with the intention to either take them to market or license them when they were approved or peri-approved. These stages are the point at which most of us imagine a product to have its greatest partnering value; risk has been eliminated and commercial sales are within sight. Let's look at these deals and see what lessons can be learned.

Once again, we will consider a Drug Delivery product deal to be one in which the Drug Delivery company partners or sells a product it has advanced, generally with its own funds, to a point of clinical validation. The product depends on a drug delivery technology to establish inherent product benefits versus the non-enhanced molecule. A product deal is distinct from the more common drug delivery deal in which the drug delivery company either licenses out its technology or is contracted, and financially supported, to apply its technology to a partner-specified pharmaceutical active.

As always, we need to be careful when valuing a Drug Delivery product deal to assess whether it involves a novel drug delivery product or a drug delivery generic (ANDA strategy). With an increasing number of innovative Drug Delivery products on the market, there is a growing opportunity to provide generics of these products when the originator loses exclusivity. These ANDA Drug Delivery products really are generics and don't fairly define the potential of innovative drug delivery or necessarily guarantee a smooth path to regulatory approval.

Note, that when disclosed, almost all reported royalties represent the highest possible rate. In the cases where a range is presented, assume that the highest rates are achieved only when the top tier of sales are reached. As reflected in this article, license fees, including upfront license fees and milestones, are much easier to find than the corresponding royalty rates. The product terms included in this article were sourced from non-confidential sources that include SEC filings, press releases, published interviews, and financial analyst reports.

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PRODUCT BENCHMARKS

Tables 1 and 2 summarize selected Drug Delivery product deals from 1999 through January 2006. Several of these deals were included in the September 2004 article. Together, there are more than 20 product deals, and they provide a good idea of the evolving value of a Drug Delivery product. The tables list the parties to the transaction, product stage at the time of the deal, total license fees (including upfront payments, equity investments, and milestone payments), and royalty rate or profit split. Each of these transactions has much more color and subtlety than can be concisely presented in this article, and the reader is encouraged to review the available information on the transactions, especially the associated SEC filings.

WHAT THE DEALS TELL US

We are starting to see some consistency in the deals. It's obvious that out-licensing a Drug Delivery product rather than a Drug Delivery technology is a far more attractive option when license fees and royalties or profit share are concerned. On the flip side of course, to get to this stage, the Drug Delivery company must invest considerable time and resources while managing development and regulatory challenges.

There is good consistency on the royalty rate for products that are either approved or in the pre-approval stage when licensed. Royalties for these products are in the range of 25% to 35%, a very attractive figure for any product, especially those that will command sales upward of $100 million per year. It's hard to rationalize creating the necessary commercial infrastructure when this type of "risk-less" reward is possible with an out-licensing option. For the licensee, these royalties can also be a bargain if one considers that R&D costs for a large company is in the range of 13% to 17% of sales. This is especially true if the royalty includes supply of product.

There is less information on royalty rates for Drug Delivery products licensed at earlier stages of development. The only figures we have are the 15% and >10% rates for the Nastech and Flamel deals. These numbers seem to be reasonable, and it's likely that products licensed at Phase II or earlier command royalty rates in the 10% to 15% range. All of these products still have an appreciable amount of risk associated with their development as well as considerable costs related to development. These royalty rates are sometimes supplemented by attractive milestone payments that are back ended and accordingly provide for a somewhat higher effective risk-adjusted royalty rate.

Looking at the more recent product deals, we can see trends emerge. The deal terms for the best of these transactions are close to terms offered for biotechnology products at comparable stages of development. To get to these valuations, the Drug Delivery products do not simply enhance the performance of the active; rather they define a whole new therapeutic solution. The Alkermes deal with Cephalon and Nastech's deal with Merck are two very good examples. Nastech's deal with Peptide YY 3-36 provides an attractive, albeit early and unvalidated, approach to the treatment of obesity. Alkermes' depot formulation of naltrexone offers a unique therapy for the management of alcoholism. Neither of these products is a simple a "once-a-day" enhancement of an approved product, both use Drug Delivery to either enable or transform the active for a unique therapeutic solution.

The Alkermes deal is very impressive and provides good support for hanging on to a product as long as possible. Their deal with Cephalon calls for an upfront payment of $160 million plus a regulatory milestone of $110 million payable upon approval by the US FDA (conditional approval was received in December). In addition, there are commercial milestones of $210 million related to achieving defined annual sales targets. All-in-all, Alkermes will receive $270 million in upfront and approval-related license fees and another $210 million for hitting sales targets, a total of almost $500 million. And this is only for half of the product rights in the US. Alkermes will co-promote with Cephalon and receive half of the profits in the US, while retaining complete rights in the rest of the world. Alkermes will however be responsible for all US development, approval, and commercial expenses through December 2007, to a maximum of $120 million.

Another strong Drug Delivery deal product involves Biovail and Ortho-McNeil for a pair of approved drug

TABLE 1 - SELECTED DRUG DELIVERY PRODUCT DEAL TERMS (1999-2003)

LICENSOR	LICENSEE	ACTIVE	TECHNOLOGY	TERRITORY	STAGE AT LICENSING	TOTAL LICENSE FEES[A]	ROYALTY
1999							
NeoPharm	Pharmacia	Paclitaxel	Injectable-Liposome	Worldwide	Ph II	$69 MM	Not disclosed
2002							
Atrix	Sanofi-Synthelabo	Leuprolide	Injectable - Depot	USA & Canada	Ph III	$60 MM	33%*
Atrix	MediGene	Leuprolide	Injectable - Depot	Europe, CES	Ph III	$20 MM	~18%
Durect	Endo	Sufentanil	Implant - SR	USA & Canada	Pre-Ph III	$57 MM	50/50 Profit Share
Nastech	Pharmacia	Apo-morphine	Nasal	Worldwide	Ph II	$53 MM	15%*
SkyePharma	Endo	Morphine	Injectable - Depot	USA & Canada	Ph III	$70 MM	20-60%
SkyePharma	Enzon	Cytarabine	Injectable - Depot	North America	Approved	$12 MM+	35% including supply
2003							
Flamel	BMS	Insulin	Injectable - SR	North America	Pre-Ph II	$165 MM	>10%*
Inex	Enzon	Vincristine	Injectable - Liposome	North America	Ph III	$75 MM	25%*
Labopharm	Multiple	Tramadol	Oral - SR	Europe	Ph III	Negligible	20%*

a – includes upfront and milestones (regulatory, patent and commercial)
* - third party estimates

delivery-enhanced tramadol formulations. The sustained release and oral disintegrating formulations are not breakthrough treatments but satisfy an important portfolio gap for Ortho-McNeil. The rewards for Biovail are largely back ended with a very attractive royalty rate that ranges from 27.5% to 37.5%, including supply. The license fee of $60 million is credited against purchases. The overall terms, while attractive, are a pay-for-performance arrangement reflecting the reality that both formulations offer little long-term exclusivity.

SkyePharma has several product deals that are interesting in the aggregate. This company has pretty much defined a tight range of terms for its specialty formulations targeting small patient populations. Typically, SkyePharma partners at the Phase III or later stage, with regional partners. Terms include an upfront of $10 to $25 million and a supply of goods at about 35% of the net sales.

TABLE 2 - SELECTED DRUG DELIVERY PRODUCT DEAL TERMS (2004-2006)

LICENSOR	LICENSEE	ACTIVE	TECHNOLOGY	TERRITORY	STAGE AT LICENSING	TOTAL LICENSE FEES[a]	ROYALTY
2004							
Nastech	Merck & Co.	Peptide YY 3-36	Nasal	Worldwide	Ph I	$246 MM	Not Disclosed (Co-promotion rights USA)
Noven	Shire	Methyl-phenidate	Transdermal	USA	Pre-approval	$75 MM	Manufacturing margin, tiered $75 MM buyout
Orexo	Endo	Fentanyl	Transmucosal America	North	Ph II	$32 MM plus commercial milestones	Double Digit Royalty
SkyePharma	First	Fenofibrate	Oral – SR	USA	Pre-approval – USA	$50 MM	25%
SkyePharma	Medeus Pharma	Morphine	Injectable - Depot	Europe	Pre-approval, USA and EU	$100 MM Euro	35-50% (Net Sales)
2005							
Depomed	Esprit	Cipro-floxacin	Oral – SR	USA	Approved – USA	$60 MM	15-25% (Royalty Minimums)
Alkermes	Cephalon	Naltrexone	Injectable - Depot	USA	Pre-approval – USA	$490 MM	Profit Share (50/50)
Biovail	Ortho-McNeil	Tramadol	Oral – SR Oral – ODT	USA (option Canada & EU)	Approved – USA	$60 MM (credit against purchases)	27.5 – 37.5% (Including supply)
Durect	Endo	Sufentanil	Transdermal	USA & Canada	Ph I	$45 MM	Not Disclosed
Impax	Dava	Oxycodone	Oral – SR	USA	Approved - USA	Up to $60 MM	Profit Share
NexMed	Novartis	Terbinafine	Topical	Worldwide	Ph I	$51 MM	Not Disclosed
SkyePharma	Mundi-pharma	Bupivicaine	Injectable - Depot	Worldwide (excluding US, Canada, Japan)	Ph II	Up to $80 MM (incl. $20 MM R&D support)	30-35% (incl. cost of goods)
2006							
Zars	Endo	Lidocaine/ Tetracaine	Transdermal	N. America	Approved - USA	$27 MM	Not Disclosed

a – includes upfront and milestones (regulatory, patent and commercial)

The success of these product deals must be balanced by a consideration of the risks in pursuing a late-stage product partnering model. Of the 10 product deals noted in the period 1999 to 2003, a total of seven are either dead or in some form of partnership or regulatory limbo. The substantial deal between Flamel and BMS has been terminated without any real explanation. This product will be hard to partner given that it had previously fallen out of an earlier partnership with Novo Nordisk. The implant formulation product that was the basis of the Durect deal with Endo seems to be undergoing technology reworking, although the parties have more recently agreed to partner on a transdermal formulation of the same active. Inex's liposomal formulation of vincristine crashed and burned at the FDA and will need a major clinical rework if it is to reach the market. On the positive side, by partnering at the Phase III stage with Enzon, Inex was able to recoup a portion, $12 million, of their development investment. Other products with regulatory or development challenges include Labopharm's tramadol sustained-release formulation and Noven's transdermal formulation of fentanyl. Two other products that have either died or undergone major reworking are Nastech's apomorphine presentation for erectile dysfunction and NeoPharm's liposomal paclitaxel formulation.

REFLECTIONS

Proceed with caution. There is a jackpot to be hit when developing Drug Delivery products through to late-stage development and approval. And the odds are much, much better than any lottery. With some imagination in product design, and by targeting an under-serviced medical need, it's possible to harness the potential of Drug Delivery to provide a breakthrough therapeutic. The biggest challenges for a drug delivery company arise in two areas. The first relates to medical expertise. Most Drug Delivery companies are primarily technology focused and have little aptitude or expertise to properly explore the medical issues and implications of a new product. This often results in companies developing "no-brainer" products that are simply enhanced versions of existing products, once-a-day versus twice-a-day, or transdermal instead of injectable. While these concepts are not too hard to conceive and reduce to an acceptable product, they generally have little or no exclusivity that can drive partnering and market value. The more visionary products, such as Alkermes' Vivitrol, Anesta's Actiq, and Alza's Duragesic, have gone a step beyond the ordinary and as a result have captured, or expect to capture, rewards commensurate with those afforded innovative biotechnology products.

The second challenge for Drug Delivery companies in developing products is related to resources. Too many companies have too few funds to be able to hang on to a product through to the point where there is a better payoff. It's not just the matter of the funds; it's a matter of risk-adjusted funds. As we saw with a number of deals consummated in the 1999 to 2003 period, there is no guarantee of reaching the next regulatory milestone, much less getting to approval. That means a Drug Delivery company will need to have a portfolio of products in development with the appropriate resources to develop all of them. It's not realistic for a company to pick the "winner" and focus its resources on that one product. Picking products, like stocks, requires skill but even the most skillful aren't able to guarantee success except with a portfolio. The necessary resources for success include more than strong funding. Having development and regulatory experience onboard is critical. Yes, it's possible to outsource development activities but only if the knowledge, if not the hands, also reside within the company. One solution of course is to partner with a company that can provide the resources, such as Nastech working with Merck for Peptide YY 3-36. This ensures that each part of the process is handled by an expert; the Drug Delivery company is focused on formulation while the BioPharma partner provides the development, regulatory, and commercial skills.

The second-generation Drug Delivery products now reaching the market are impressive. These are not "accidental" products that failed an earlier partnership or weren't able to secure a partnership until later. Biovail's Ultram ER and ODT, as well as Alkermes' Vivitrol are well-conceived and well-executed products that are rewarding their owners while validating a business model for profitability in Drug Delivery. ♦

Optimizing Outsourcing Relationships in Formulation Development: A Matter of Trust

By: Contributor Cindy H. Dubin

According to industry estimates, outsourcing drug development — considered to be the heart of pharmaceutical and biotech companies — is growing at a yearly clip of 15% to 20%. This past year, pharmaceutical companies worldwide spent nearly $2 billion doling out parts of the drug research process, mainly to US specialists. By 2007, spending should reach $6 billion, according to a report by research firm Kalorama Information. The largest outsourcers, who account for 25% of the outsourced drug discovery spending, are Big Pharma companies like Pfizer, Merck, Novartis, Bristol-Myers Squibb, and Eli Lilly.

The US pharmaceutical industry already spends an estimated $14.5 billion annually on outsourcing the manufacturing, formulation, and packaging of drugs. The growth in outsourcing parts of the drug discovery process is being fueled primarily by two factors, according to the Kalorama report. First, most drugs marketed so ferociously today were not actually discovered by the company doing the marketing. Second, the relatively new fields of genomics and proteomics have produced a host of new drug targets — too many to work on all of them in-house at even the largest drug companies. It can also be faster and cheaper to have discovery work done outside of the company. For now, much of the drug discovery outsourcing work will likely go to specialty drug discovery companies or biotech firms in the US.

FORESIGHT & FORMULATION

MDS Pharma Services boasts a successful formulation team that has found the right ingredients to forging an optimal outsourcing relationship. Brian R. McMillan, Section Head of Formulation Development at MDS, explains his three-pronged procedures to a typical formulation process. The first is client communication. "We initiate each project with a very thorough discussion of the client's objectives. We want to try to understand everything they want to achieve with a formulation."

Second, a collaborative relationship is key. "Clients usually already have a dosage form in mind, but often haven't decided on precise specifications," says Mr. McMillan. "Together, we will explore the options. Sometimes the client knows what they want, right down to the smallest detail."

He describes how he was once working on a placebo tablet for an NDA clinical trial that would be dosed alongside the innovator product. The client wanted the placebo to be physically identical to the innovator in virtually every respect — color, shape, size, weight, feel, and taste. The products would differ almost undetectably so that researches could tell them apart.

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Finally, MDS relies on its scientific expertise. "When beginning a new project, we prefer to evaluate samples of the API from multiple lots," says Mr. McMillan. "Because lots can vary in physical and chemical attributes, with different particle sizes, densities, surface areas, solubilities, flow properties, etc, if a production process is developed based on one set of characteristics, it may not work well if the characteristics are different, especially if the API is going to take up a large percentage of the final dosage form. So, we cover all of the details up front to ensure that the API's physical properties are optimal and will be uniform from lot to lot once studies begin. We work with the client to create a dosage form that appears chemically and physically robust enough to maintain its potency and physical characteristics throughout manufacturing. Once the client is satisfied, we develop a set of process characterization protocols and scale-up production to test and refine a manufacturing process."

SELECTING & MONITORING CROs

Whether outsourcing formulation or other aspects of the drug development process, careful selection and monitoring of a provider are necessary to ensure that the research studies are conducted as designed and are completed on time and within budget. According to Duane B. Lakings, President of Drug Safety Evaluation Consulting, Inc., Elgin, Texas, the use of a CRO in nonclinical drug development programs, or outsourcing, is a common practice. Presently, more than 450 CROs exist in the US and Europe, with some offering a complete drug development support system, from synthesis of the drug substance to conducting Phase III safety and efficacy human trials. Others specialize in such areas as pharmacology animal model development and implementation, formulation development and stability testing, bioanalytical method development and validation, and clinical trial study support.

A company wanting to outsource must first identify a lead that mediates a human disease process and then needs to conduct the GLP-regulated research studies to first obtain an IND and then for an NDA submission. The drug development project team (DDPT) is commonly charged with coordinating the outsourcing program. For a small biotechnology firm, this responsibility may fall on the shoulders of a single individual or a small group. Mr. Lakings identifies three key elements to a successful outsourcing program:

1. The first requirement for a successful outsourcing program is to identify which studies or aspects of the development program are to be outsourced and the project timelines for the initiation and completion of these studies so the results and study reports are available for decision-making and regulatory agency submissions. A drug development plan provides much of this information.

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2. Sub-project teams, consisting of DDPT members, identify and then select the appropriate provider to conduct the desired research studies. These teams are also responsible for monitoring the contractor to ensure that the studies are being conducted as designed and that the generated results are appropriately recorded and documented in study reports. "Subteams give a project a deeper focus," says Jack Aurora, PhD, Director, Pharmaceutical Research and Development, at PharmaScience, Inc., in Montreal, Canada. "They ensure that nothing falls between the cracks."

Teams should prepare study designs for each of the research studies to be outsourced, providing enough information for the providers to generate a draft study protocol and a proposal with time and cost estimates. As an example, commonly included items for a nonclinical pharmacokinetic study design might include: Study Purpose; Test Species or Animal Model; Test Article or Drug Substance; Route of Dosing; Frequency of Dosing; Administration Technique; Number of Animals; Specimens to be Collected and Time of Collection; Bioanalytical Method; Stability of Test Article; Analyses; and Projected Timeline for Study Start and Completion.

"We expect our clients to be open with us and think out their projects well ahead of time," explains Matthew Augustine, PhD, Vice President R&D, Harmony Labs, Inc., a contract manufacturer in Landis, North Carolina. "Those who do not can end up spending their time and money unwisely."

The proposals should be evaluated and culled down to only those contractors that the team wants to further evaluate. At times, providers will recommend modifications to the design, which may or may not improve the overall study and could provide additional information on the drug candidate. When this occurs, the sponsor needs to critically evaluate the expanded study to ascertain if the increased costs and possibly extended study duration justify the additions.

The team should visit the candidates' sites to ensure qualifications and that the provider has the facilities and personnel necessary to conduct the studies. Commonly, these site visits include assessments of GLP compliance, SOPs, and computer validation.

Those contractors on the now short list should be asked to provide their "best and final" cost as well as the dates when they can actually initiate the study and the date when they project the draft final report will be available for review. Finally, a provider is chosen.

3. It is essential to monitor the supplier to ensure that the research studies are conducted according to the study protocol, that the results are obtained using appropriate techniques and procedures, and that the generated data are correctly recorded and documented in the study report. Monitoring studies at the provider end should include, but are not be limited to reviewing and approving the study protocols (prepared by the contractor and detailing the procedures to be followed to successfully complete the study designs); monitoring various aspects during the research phase of each study to ensure that the data collected is appropriately documented and does not contain "surprises" that can prevent the results from being used to support submissions to regulatory agencies; assisting in the evaluation and interpretation of results to ensure the data is analytically acceptable and correctly correlated to tell the story of the experimental results; and reviewing the study report to ensure that the information provided accurately reflects the generated results, documents any deviation from the study protocol, and gives appropriate conclusions.

"The client must take an active role in the project to keep the project on schedule and resolve any problems that may occur," says Dr. Augustine. "Every project has idiosyncrasies and mistakes can happen, but they should be dealt with quickly."

SUMMARY

By carefully evaluating an outsource provider and then effectively working with these organizations during and after the study, a company can obtain the desired information needed to successfully characterize their drug candidate and prepare the necessary submissions to regulatory agencies. A close partnering between the company and the provider is very important to ensure that the outsourced research studies are conducted as designed, within the desired time frame, and for the budgeted amount.

"We meet or exceed most timetables, but on occasion, we miss our original timeline and then have to readjust the timeline accordingly," says Dr. Augustine. The client must understand that as a contractor, we have their best interest at heart. It's a matter of trust."♦

BIOGRAPHY

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

Attorney REVIEW

Product Life Cycle Management Strategies & Enforceability of Product Extension Patents

By: Sam L. Nguyen, PhD, Associate, Heller Ehrman LLP

BIOGRAPHY

Sam L. Nguyen, PhD is an Associate with Heller Ehrman LLP, a law firm with more than 700 attorneys in 12 cities nationwide and abroad. Dr. Nguyen is a member of Heller Ehrman's Life Sciences Practice Group and the Patents & Trademarks Practice Group. Dr. Nguyen's practice focuses on domestic and international patent prosecution, and counsels clients on strategic aspects of patent laws.

In today's highly regulated and competitive pharmaceutical markets, brand name manufacturers or innovators, Biotechnology companies, Specialty Pharmaceutical companies, as well as some generic pharmaceutical companies with basic research programs, should all have well-formulated product life-cycle management strategies. Typically, these strategies should be directed toward highly focused research and development efforts that are coordinated with the companies' strategies for protecting its intellectual property.

Because innovators take on significant economic risks when they embark on the research for new and useful pharmaceutical products for the treatment of diseases, innovators have an interest in protecting their commercial products from competitors. Innovators must also recover the significant investments associated with identifying, developing, and obtaining FDA approval of useful product candidates. Overall, it may take anywhere from 2 to 12 years (or longer) to obtain approval for a single product. One important aspect for maintaining and maximizing exclusivity for the innovator's product is to establish and execute a well-defined global patent filing strategy.

Companies typically seek patent protection for the drug product by securing claims covering the newly discovered biologically active compound (NCE). In conjunction with securing genus, subgenus, and species claims directed to the composition of matter, innovators should also seek claims directed to the various methods of preparing the compound, the intermediates, and the penultimate step(s) for the method of preparing the product. Novel manufacturing processes may provide important protection for the final product, particularly when the new process produces a more stable product and/or a product with higher purity.

Because patent applications for NCEs are typically filed several years before an innovator obtains regulatory approval for the marketing of a pharmaceutical product, the maximum patent term of 20 years of commercial exclusivity for a pharmaceutical product is not attainable. Patent holders may recover a portion of the loss of the patent term by receiving a patent term adjustment (PTA) for administrative delays in the issuance of the patent by the USPTO and/or by applying for patent term extensions (PTE) to compensate for any regulatory delay in the approval of products. In addition, companies may obtain other regulatory exclusivities for a particular product, including 5-year "data exclusivity" for NCEs, 3-year clinical study exclusivity for new products or new uses, 7-year orphan drug exclusivity, and 6-month pediatric extensions of patents and the foregoing exclusivities.

PRODUCT EXTENSION PATENTS

There are a number of different strategies for brand-name manufacturers or innovators to maximize the product life cycle of a brand product containing an active pharmaceutical compound. Innovators may establish various strategies for developing and patenting novel compositions, formulations, and method of use of the compositions that may result from unexpected improvement in the pharmacokinetics. Such improvements may include, for example, an improved bioavailability profile, efficacy and/or reduction of undesired side effects, and improved patient convenience and compliance.

Patentable innovations for novel compositions of a commercial product may include a variation in the product composition, including alternative salts, hydrates, solvates, esters, derivatives, metabolites, stereoisomers, and crystalline polymorphs of a drug product, or their combinations. Novel formulations comprising the drug product may be patentable where the formulation may be specifically formulated or adapted for different methods of drug delivery. These formulations may

include the employment of novel excipients or combination of excipients that affect the pharmacokinetics of the composition, such as excipients that provide unexpected extended release of the active compound. Extended-release formulations may provide fewer side effects and may require less frequent administration. Different excipients may include the use of different vehicles, stabilizers, solubilizers, surfactants, and solvents, and their various combinations.

Innovators may also consider research opportunities for establishing new and useful dosage forms, line extensions, or proprietary delivery technologies. The discovery of novel method of use may include establishing a different route of administration or delivery, different dosage forms and dosage regimens, and new product combinations. Different route of delivery may include oral delivery (controlled or sustained release), nasal, liposomes, injectables (IM, IV), implants, depots, polymers, micelles, pulmonary, passive and active transdermal systems, transmucosal, ocular, rectal, and vaginal delivery methods.

ENFORCEABILITY OF PRODUCT EXTENSION PATENTS

The criteria for patentability of an NCE are the same as it is for a follow-on or product extension invention: To be patentable, the invention must be novel, useful, and unobvious. Pharmaceutical patents may be challenged as being invalid or unenforceable on a number of grounds, including invalidity based on prior art, on-sale bar, indefiniteness, obviousness, inherent anticipation, double patenting, and inequitable conduct. While follow-on or product-extension patents may be invalidated under these same grounds, product-extension patents typically face additional potential invalidating hurdles not faced by patents on NCEs. In particular, extension patents may be challenged on grounds of obviousness based on patents and non-patent publications that are associated with the NCEs that are invariably published before the filing of the product-extension patent applications.

Patents claiming pharmaceutical products are closely scrutinized by potential generic competitors who aggressively use the specialized statutory mechanisms of the Hatch-Waxman Amendments to challenge potentially weak or narrow patents in order to bring lower cost versions of branded drugs to market as early as possible. Many types of follow-on patents (formulation, polymorphs, etc) are narrow enough that generics can design around them to create a therapeutically equivalent non-infringing product. New method-of-use patents may also be avoided because generic firms are permitted to omit patented indications from the labeling of their generic products when there are other unpatented indications for the drug.

Table 1 provides selected examples of recent and pending litigation involving pharmaceutical follow-on patents challenged by generic companies, and illustrates that such patents can and do meet their demise when challenged. Further highlighting this point, a July 2002 Report by the Federal Trade Commission study on Generic Drug Entry Prior To Patent Expiration, the FTC found that out of 104 generic drug applications that challenged a patent on the branded drug, the generic applicant prevailed 73% of the time (22 cases), the innovator prevailed 27% of the time (8 cases), and 38% of the cases settled (20 cases). The FTC report also noted that of the 104 generic patent challenges, 29 patent holders never filed suit while 75 patent holders did file suit, and of the 53 cases that were resolved, 2 cases had patents that expired before litigation was resolved, and in one case, the NDA was withdrawn before litigation was resolved.

Given the potential enforceability weaknesses of any one patent, pharmaceutical innovators should develop a broad-based patent portfolio strategy to maximize the chance of success on at least one such patent, and thereby optimize product lifecycles.

SUMMARY

Pharmaceutical companies should have well-formulated product life-cycle management strategies to ensure that their significant investment in their valued commercial products are well protected by a comprehensive patent portfolio. Pharmaceutical companies should identify and capitalize upon all opportunities for maximizing patent terms and exclusivities for NCEs and for follow-on products in order to optimize the company's franchise as provided by law. ♦

Table 1. Selected Product Extension Patents

Parties	1. Product; Extension Technology 2. Issues Litigated	Disposition
Glaxo v. Novopharm	1. Zantac (ranitidine); polymorph forms 2. Invalidity due to anticipation; federal antitrust and state unfair competition laws	Patent not infringed
Aventis v. Barr Labs	1. Allegra (fexofenadine); wet granulation process, microcrystalline cellulose compositions; bilayer tablets 2. Invalidity; Non-infringement	5 patents under litigation
Abbott Laboratories v. Baxter Healthcare	1. Ultane (sevoflurane; water as stabilizing additive 2. Non-infringement	3 patents under litigation
Purdue Pharma v. Endo Pharms., Inc.	1. Oxycontin (oxycodone) controlled-release formulation with specific dosage and plasma concentration profile for improved titration; method of use 2. Invalidity due to inequitable conduct	Patents infringed; 3 patents invalidated
Glaxo Welcome v. Andrx	1. Wellbutrin SR and Zyban (bupropion hydrochloride); sustained-release formulation 2. Non-infringement	Vacated for further review
Pfizer Inc. v. Ranbaxy	1. Lipitor (atorvastatin); sustained-release formulation 2. Invalidity due to double patenting, obviousness, anticipation and inequitable conduct	Not invalid; under appeal
Eli Lilly v. Dr. Reddy Labs	1. Zyprexa (olanzapine); compound and method of treatment 2. Invalidity due to obviousness, double patenting, inequitable conduct, novelty, and public use	Valid
Alza v. Mylan	1. Ditropan XL (oxybutynin) 2. Invalidity due to anticipation and obviousness	Invalid; under appeal

EXCIPIENT UPDATE

Carbopol®: A Versatile Polymer

By: Manish Patel, MPharm; Bhavik Patel, MPharm; Ritesh Patel, MPharm; Jayvadan Patel, PhD; Praful Bharadia, PhD; Madhabhai Patel, PhD

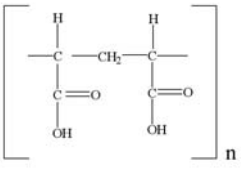
ABSTRACT

Carbopol is a synthetic high molecular weight cross-linked water-soluble polyacrylic acids polymer. Available in different viscosity grades, Carbopol polymers are used in controlled- release tablets; as a bioadhesive in buccal, ophthalmic, intestinal, nasal, vaginal, and rectal applications; and as a thickening agent in oral suspensions. It is safe and effective; non-sensitizing; has no effect on the biological activity of the drug; and has excellent thickening, suspending, and emulsification properties for topical formulations. Carbopol also has a valuable position in the personal care products market. Tablet formulations using Carbopol polymers have demonstrated zero-order and near zero-order release kinetics. These cross-linked polymers of acrylic acid provide excellent suspending ability for insoluble ingredients, and virtually eliminate the problem of settling, even when used at very low levels.

INTRODUCTION

Carbopol features a wide derivative of synthetic high molecular weight cross-linked water-soluble polyacrylic acids, which confirms to USP/NF specification as Carbomer.[1] It has an average equivalent weight of 76, and the general molecular structure can be as follows:

STRUCTURE



Carbopol is available as a white free-flowing powder. It is a water-soluble, macromolecular compound having a high affinity to water, alcohol, and glycol. When dissolved in such solvents, optionally followed by neutralization with an alkali, it provides a highly transparent, highly viscous, gel-like, thixotropic liquid having a high-yield value even in a low concentration. Compared with other neutral and synthetic water-soluble polymers, Carbopol is superior in certain immensely useful performance characteristics. It has an ability to increase viscosity, stabilize dispersions, and resist aging and mold growth. Carbopol is available in different grades, which can be used for specific applications as per requirements.

Carbomer 934, Carbomer 934P, Carbomer 940, Carbomer 941, and Carbomer 1342 are listed in the USP.[1] The viscosities of neutralized 0.5% aqueous dispersions of Carbomer are provided in Table 1.

CHARACTERISTICS & BENEFITS

High viscosity can be obtained by dispersing (by swelling) Carbopol in diluents, such as water and alcohol or glycol and terminal neutralization with an alkali. It produces a powerful viscosity-increasing effect even when small amounts are added. Other characteristics and benefits of Carbopol include:

- Thixotropic viscous liquids with high-yield value can be obtained.
- Viscous liquids having good emulsion stability and solid dispersion stability can be obtained.
- provides an excellent transparent viscous liquid.

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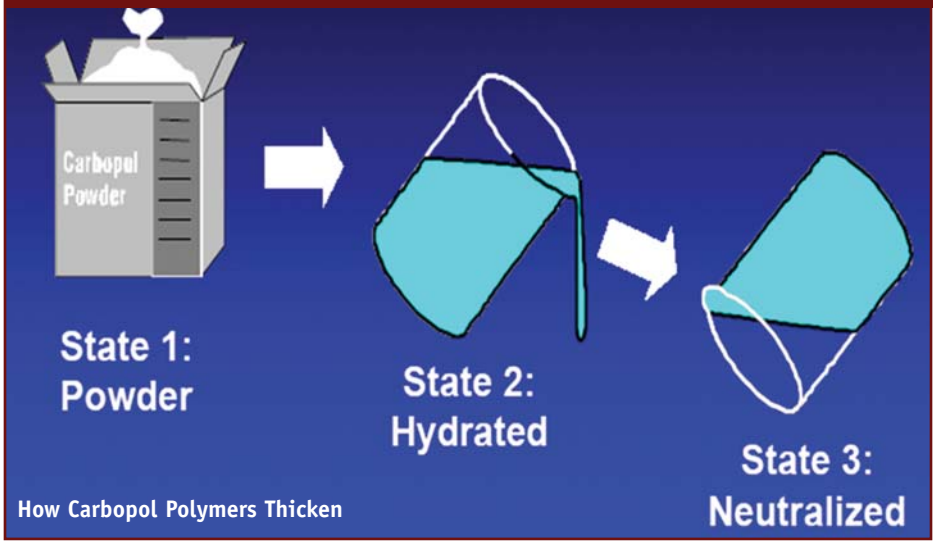
FIGURE 1



- In spite of its ability to afford high viscosity, it does not rope or stick. So stirring and pumping/injecting is also possible.
- Can be used in a wide range of pH values.
- Is a synthetic product; has resistance to hydrolysis and oxidation.
- Is stable against temperature change.
- Is non-toxic and a USP/NF-grade product.
- Has excellent shelf-life.
- Has uniform performance and reproducibility.

TYPES OF CARBOPOL

Carbopol 940

Carbopol 940 forms sparkling clear transparent gel with water or hydro-alcoholic medium. It is suitable for use in making high-viscous liquids or gel for cosmetics and external use in medium preparations. It is the most efficient thickener of all the Carbopols and has extremely short flow properties.

Carbopol 934

Carbopol 934 can be used in thick formulations, such as viscous gels, thick emulsions, and heavy suspensions. It provides permanent stability at high viscosity. In an aqueous system, Carbopol 934 exhibits short flow properties, which are of interest in applications such as cosmetics and spray-ons.

Carbopol 934P

Carbopol 934P is specially tailored for the pharmaceutical industry. It can be useful for internal pharma dosage forms. Carbopol 934P is high-purity grade and used for thickening, suspending, and emulsifying. It is also useful in tablets for binding and sustained-release formulations.

Carbopol 941

Carbopol 941 provides permanent emulsion and suspensions at low viscosities. The gels are produced with excellent clarity. In the hydrogen-bonding thickening mechanism, it is more effective than other Carbopols. It is useful for cosmetics and for emulsion stabilization.

Carbopol 910

Carbopol 910 is effective at very low concentrations, when a low viscosity is required. It features low-ion sensitivity, and its flow property has a slow recovery, which permits good leveling. It is useful for the paint and coating industries as well as for cosmetic and skin care applications.

Carbopol 907

Carbopol 907 is the only liner polymer that provides good water solubility and lubricity without viscosity. It is used in applications requiring high content without appreciable increases in viscosity. Film can also be prepared by adding plasticizer (ie, PEG6000, PEG4000), triethyl citrate, etc.

PHYSICAL & CHEMICAL PROPERTIES

Carbopols are different in performance, but their general properties are the same (Table 2). Carbopol is a replacement for sodium carboxymethyl cellulose (CMC), all gums, xanthane gum, sodium alginate, poly-acrylic acids, etc. It thickens with a wide range of flow properties, suspends insoluble ingredients, stabilizes emulsions, and controls release.

Carbopol rheology modifiers are proven as exceptional thickeners, suspending agents, and stabilizers, utilized in a wide variety of personal care products. Used at concentrations lower than 1%, they offer the flexibility to develop products with a wide range of flow and rheological properties. Carbopol polymers are available as powders and liquid.

Carbopol polymers are polymers of acrylic acid cross-linked with polyalkenyl ethers or divinyl glycol. They are produced from primary polymer particles of about 0.2 to 6 microns (average diameter). The flocculated agglomerates cannot be broken down into the ultimate particle when produced. Each primary particle can be viewed as a network structure of polymer chains interconnected by cross-links. Without the cross-links, the primary particle would be a collection of linear polymer chains intertwined but not chemically bonded. Carbopol polymers, along with Pemulen® and Noveon® polymers are all cross-linked. They swell in water up to 1000 times their original volume (and 10 times their original diameter) to form a gel when exposed to a pH environment greater than 4.0 to 6.0. Because the pKa of these polymers is 6.0 to 0.5, the carboxylate groups on the polymer backbone ionize, resulting in repulsion between the negative charges, which adds to the swelling of the polymer. The glass transition temperature of Carbopol polymers is 105°C (221°F) in powder form. However, the glass transition temperature decreases significantly as the polymer comes into contact with water. The polymer chains start gyrating, and the radius of gyration becomes increasingly larger. Macroscopically, this phenomenon manifests itself as swelling.

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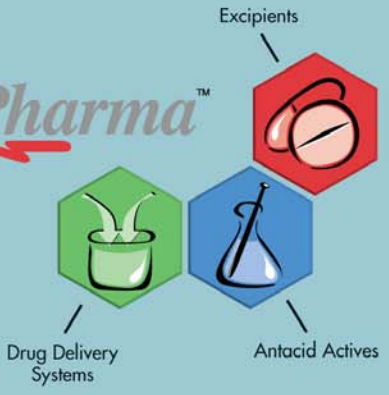

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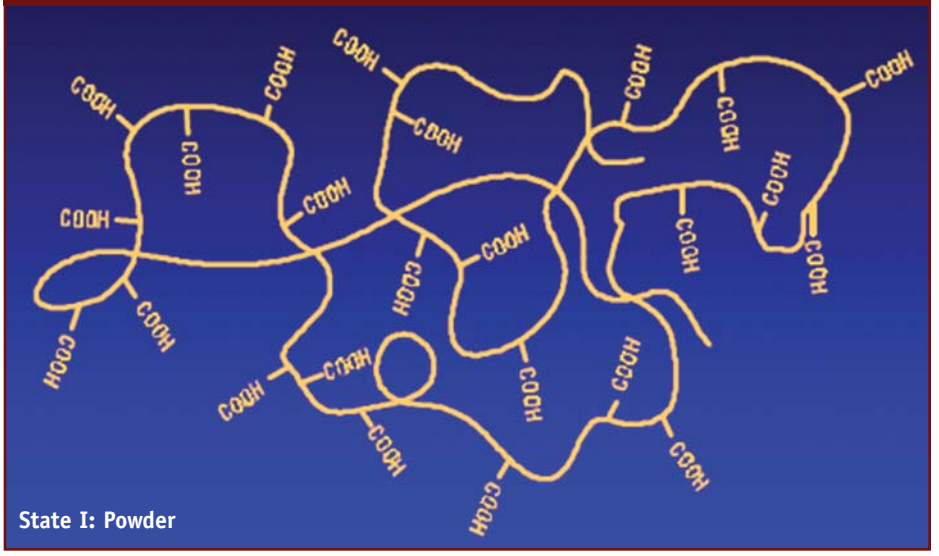
FIGURE 2



Carbomer grades with no residual benzene content, such as Carbopol 971P & 974P, may be used in oral preparations, suspensions, and tablets and certainly in topical preparations.[2] Carbopol 974P NF and 971P NF are polymerized in ethyl acetate, and it is for this reason they are a toxicologically preferred alternative to Carbopol 934P NF resin. Carbopol 974P, like Carbopol 934P, is a highly cross-linked polymer, whilst Carbopol 971P is a lightly cross-linked polymer.[3]

Carbopol is very useful as a major component of drug delivery gel systems for buccal, transdermal, ocular, rectal, and nasal applications.[4-7]

The readily water-swellable Carbopol polymers are used in a diverse range of pharmaceutical applications to provide the following:

- Controlled release in tablets. Carbopol polymers offer consistent performance over a wide range of desired parameters (from pH-derived semi-enteric release to near zero-order drug dissolution kinetics) at lower concentrations than competitive systems.
- Bioadhesion in buccal, ophthalmic, intestinal, nasal, vaginal, and rectal applications.
- Noveon AA-1 USP polycarbophil is the recognized industry standard for bioadhesion.
- Thickening at very low concentrations (less than 1%) to produce a wide range of viscosities and flow properties in topical lotions, creams and gels, oral suspensions, and in transdermal gel reservoirs.
- Permanent suspensions of insoluble ingredients in oral suspensions and topicals.
- Emulsifying topical oil-in-water systems permanently, even at elevated temperatures, with essentially no need for irritating surfactants.

APPLICATIONS OF CARBOPOL IN PHARMACEUTICAL FORMULATIONS

The applications of Carbopol in pharmaceutical formulations include us as a bioadhesive agent, emulsifying agent (0.1% to 0.5%), release-modifying agent, suspending agent (0.5% to 1.0%), tablet binder (5% to 10%), and viscosity-increasing agent (0.5% to 2.0%).[2,3,10,16,20,32]

BIOADHESIVE APPLICATIONS

Bioadhesion has increased applications of polymers in different dosage forms. Carbopol has versatile applications in different drug delivery formulations because of higher bioadhesion. Bioadhesion increases contact time of bioadhesive dosage forms with the absorbing tissue, eg, to reduce the nasal clearance and improve nasal drug absorption, bioadhesive microspheres were used. A Carbopol gel base improves the absorption of insulin and calcitonin in rats. Carbopol has potent applications in buccal modified-release formulations (due to the increasing mucoadhesion) and produce sustained-release characteristics. It also increases the bioavailability of ophthalmic, buccal, intestinal, rectal, and vaginal formulations.

ORAL FORMULATION APPLICATIONS

Carbopols are mainly used in oral formulation as suspending- or viscosity-increasing agents. Carbopol, having low residual benzene content, such as 934P, 971P, or 974P, may be used in oral preparations. In tablet formulations, Carbopols are used as dry or wet binders and as rate-controlling excipients.

TOPICAL APPLICATIONS

Carbopol is a high molecular weight polymer that contains carboxylic acid groups. Carbopol grades have favorable rheological properties for topical applications. The gels undergo plastic flow and have temperature-stable viscosity. Gels are formed on neutralization between pH 5 and pH 10. Neutralization expands the long chains of Carbopol by charge repulsion to produce an entangled gel network. Viscosity and gel strength depend on pH and salt content. The veterinary product, Demoso (Syntex Animal Health, Inc.), is a topical gel consisting of Carbopol 934 and 90% dimethyl sulfoxide. A Carbopol gel has good optical clarity and can be used in ophthalmic preparations. Carbopols are also employed as emulsifying agents in the preparations of oil-in-water emulsions for external use.

Carbopol's thickening mechanisms (Figures 1 to 4)[32] include (1) space filling by swollen microgels; (2) neutralization by inorganic (eg, NaOH) or organic (eg, TEA) bases (this is the major mechanism for thickening with Carbopol polymers); and (3) hydrogen bonding.

THE ADVANTAGES

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Consumers view multi-phase, multi-compartment capsules as having a higher perceived value than ordinary tablets, capsules and soft gels.

Choice of HPMC or Gelatin Capsules
With multi-phase, multi-compartment capsules you are not limited to just gelatin (animal-based product) but have the option of natural HPMC (hydroxypropyl methyl- cellulose) and alternative capsule materials.

Better Visual Appeal
Multi-phase, multi-compartment capsules have none of the dust and residue associated with powder capsules. Better visual product appearance translates to higher perceived value.

Increased Absorption and Bioavailability
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

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FIGURE 3

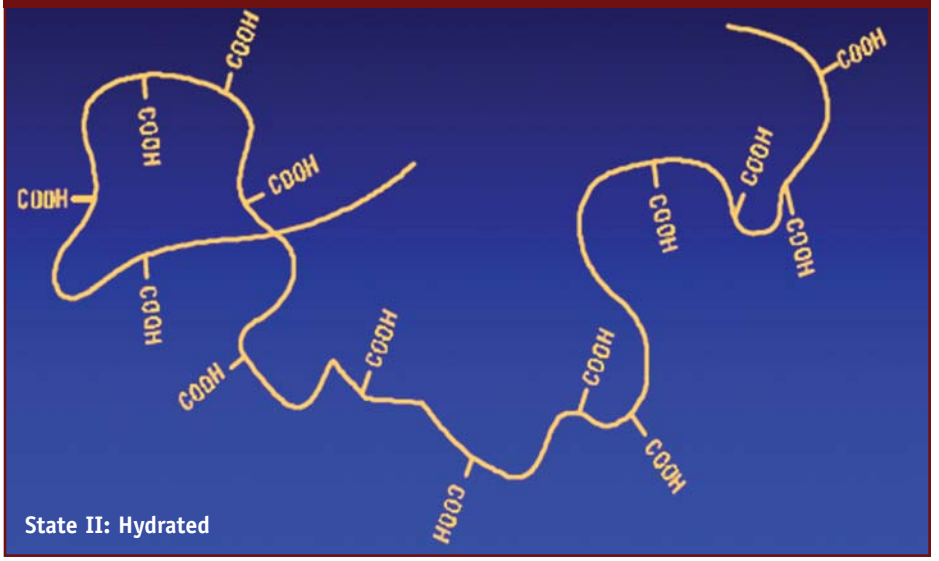

Table 1. The Viscosities of Neutralized 0.5% Aqueous Dispersions of Carbomer

Carbomer Grade	Viscosity in CPS
Carbomer 934	30,500 – 39,400
Carbomer 934P	29,400 – 39,400
Carbomer 940	40,000 – 60,000
Carbomer 941	4000 – 11,000
Carbomer 1342	9,500 – 26,500

Before contact with water, cross-linked polyacrylic acid is tightly coiled. When it is dispersed in water, cross-linked polyacrylic acid begins uncoiling. Neutralization with a base creates negative charges along the backbone. These repulsive forces uncoil polymers into an extended structure. Carbopol polymers are used to permanently suspend the active ingredients in transdermal reservoirs as well as in topical gels and creams. Pemulen polymeric emulsifiers can be used to prepare stable emulsions, such as turpentine liniment, without the use of surfactants. Carbopol polymers and Pemulen polymeric emulsifiers are often the thickener and emulsifier of choice in topical lotions.

MODIFIED-RELEASE APPLICATIONS

Since the inception of the carbomers in 1957, a number of extended-release tablet formulations involving the use of carbomer matrices have been patented.[33,34] Hudson used Carbopol 934 as a binder in sustained-release tablet formulations.[35] In another report, carbomer matrix tablets showed to follow a zero-order release mechanism in most of the cases studied.[36] Marcos et al studied the release profiles of atenolol-carbomer hydrophilic matrix tablets.[37] According to them, drug-release profiles fitted Higuchi's square-root kinetics, and the compression force had no effect on drug release. Several other investigators also studied the release kinetics from the carbomer matrix tablets.[38,39] They found that these matrices exhibited a zero-order drug release at several different concentrations of polymers.

For the controlled release of drugs, Carbopol has been studied as a matrix material directly compressed together with hydroxypropylcelluose or hydroxypropylmethylcellulose in tablets and for a solid dispersion. However, there are few reports on the application of Carbopol as a coating material.[40-49]

The Physician's Desk Reference lists three commercial tablets, EntexLA, Dospan, and Sorbitrate SA tablets, which contain carbomer polymers for controlled drug delivery. A few publications indicate their use in oral dosage forms, including matrix tablets, osmotically controlled tablets, and buccoadhesives.[50] Carbomers that are recommended for oral use as sellable controlled-release tablets include Carbopol 934P NF, Carbopol 974P NF, and Carbopol 971P NF. Manuel et al prepared amoxicillin sustained release from matrix tablets containing different proportions of Carbopol 971P NF. They reported that tablets with Carbopol 971P NF proportions of 30% to 40% produced matrices in the vicinity of an apparent zero-order release.[51]

Tablet formulations using Carbopol polymers have demonstrated zero-order and near zero-order release kinetics.[52-55] These polymers are effective at low concentrations (less than 10%). They also produce tablets of excellent hardness and low friability over a range of compression forces and produce a sustained-release effect at lower concentrations than other controlled-release excipients. They are useful at low levels (1% to 3%) as binders, improving hardness and friability at normal compression pressures and allowing target properties to be achieved at lower compression pressures. At higher levels (5% to 25%), they achieve modified or even zero-order controlled release of actives, but the powder flow

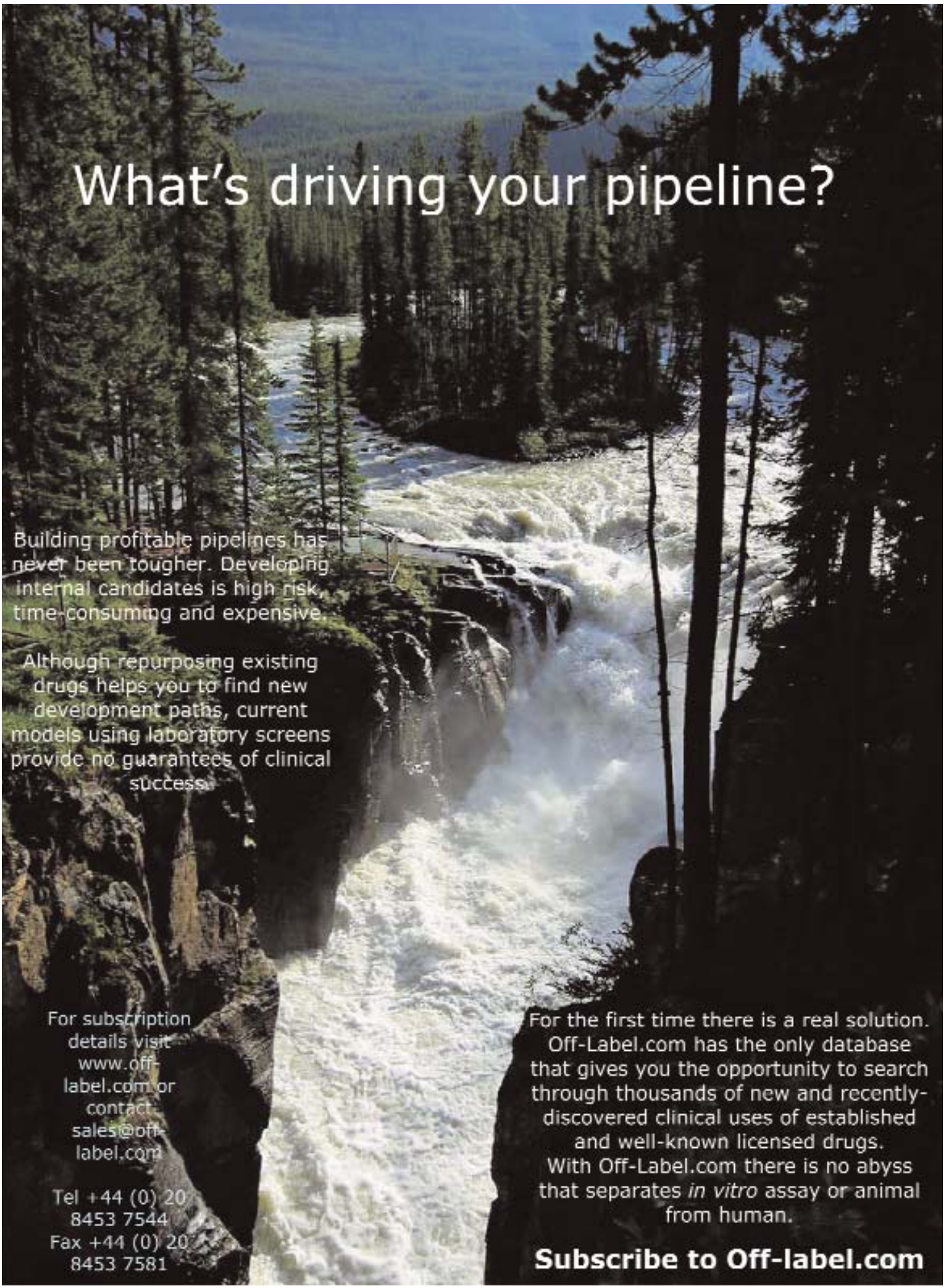
What's driving your pipeline?
Building profitable pipelines has never been tougher. Developing internal candidates is high risk, time-consuming and expensive.
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Table 2. General Properties of Carbopol

Parameters	Description
Appearance	Fine free flowing white powder with slight specific odour.
Bulk density	0.2 - 0.22 gm/ml
Specific gravity	1.41
Moisture content	2.0% max
Equilibrium moisture content	8% - 10% at humidity 70% RH & temp.30 °C
PH of 1% W/V dispersion	2.5% - 3.0%
PH of 0.5% W/V dispersion	2.7% - 3.5%
Equivalent weight	76
Ash content	0.01%
Glass transition temperature (Tg)	100 °C -105°C
Carboxyl content	56% - 67 %
Heavy metals	< 20 ppm
Arsenic content	< 1.0 ppm
Benzene content	< 0.5% (for 940, 934, 941, 907, 910) < 0.01% (for 934 P)
Free monomer content	< 0.01 %
Viscosity	RVT Brookfield viscosity cp. With 20 rpm spindle, 25 °C neutralized solution in distilled water

properties of these formulations make them intractable for a high-speed press, and they require granulation.

Jabber Emami et al has reported that matrix of lithium carbonate containing 15% Carbopol exhibited suitable release kinetics and uniform absorption characteristics. The sustained-release behavior of tablets containing 15% Carbopol prevents high blood peak levels and can be given twice to promote patient compliance during maintenance therapy.[56] Efentakis et al developed and evaluated an oral multiple-unit and single-unit hydrophilic controlled-release system containing furosemide using Carbopol 974P. They proved that Carbopol preparation exhibited great resistance to erosion, resulting in much slower drug release. This phenomenon can be attributing to Carbopol characteristics and especially to strong entanglement due to its crossed-linked structure.[57] Aboofazeli et al investigated the optimization of release profiles of lithium carbonate from a matrix-type tablet containing Carbopol, Pemulen, and EUDRAGIT RLPO, which are capable of producing tablets with desirable release patterns at concentrations of 2%, 1.5%, and 3%, respectively. Carbopol 974P showed the slowest release pattern.[58] Seyed Alireza and Reza had investigated the effect of Carbopol on the release of proparnolol HCL from tablet matrices. They reported that Carbopol 971, Carbopol 974, and Carbopol 934 were suitable for this purpose at concentrations of 14%, 16%, and 12%, respectively. Tablets containing Carbopol 971 were found to have the slowest profiles of drug release, while Carbopol 934 containing tablets had the greatest drug-release profiles among the Carbopols investigated.[59] Usefulness of certain varieties of carbomers in the formulation of hydrophilic furosemide matrices were investigated by Perez-Marcos et al.50 The coating to obtain the controlled release generally requires a coating ratio of 5% to 15%.[60-63] Therefore, controlled release could be achieved with a smaller amount of coating by using Carbopol as a coating material.

REGULATORY STATUS

Carbopol is included in the US FDA inactive ingredients guide (oral; suspension; and tablet, ophthalmic, rectal, and topical preparations), is used in non-parenteral medicines, and licensed in Europe. The Noveon polycarbophils and calcium polycarbophils are classified as category 1 GRAS (Generally Recognized As Safe) material. The toxicity of Carbopol polymers has been summarized by the Cosmetic Ingredient Review Expert Panel.[64] As a result of the intensive testing and the properties of Carbopols, they have gained wide application in a variety of pharmaceutical and other formulations. Some of the marketed applications are shown in Table 3.

SUMMARY

Carbopol polymers are polymers of acrylic acid cross-linked with polyalkenyl ethers or divinyl glycol. They are available in different grades and have been extensively used in the pharmaceutical and cosmetic industries. Carbopol polymers are used successfully in controlled-release tablets, as a bioadhesive in buccal, ophthalmic, intestinal, nasal, vaginal, and rectal applications, and as a thickening agent in oral suspensions. They are safe and effective and non-sensitizing, having no effect on the biological activity of the drug. Products with a wide range of viscosities and flow properties have been successfully formulated and commercialized. Carbopol polymers are used to permanently suspend the active

FIGURE 4

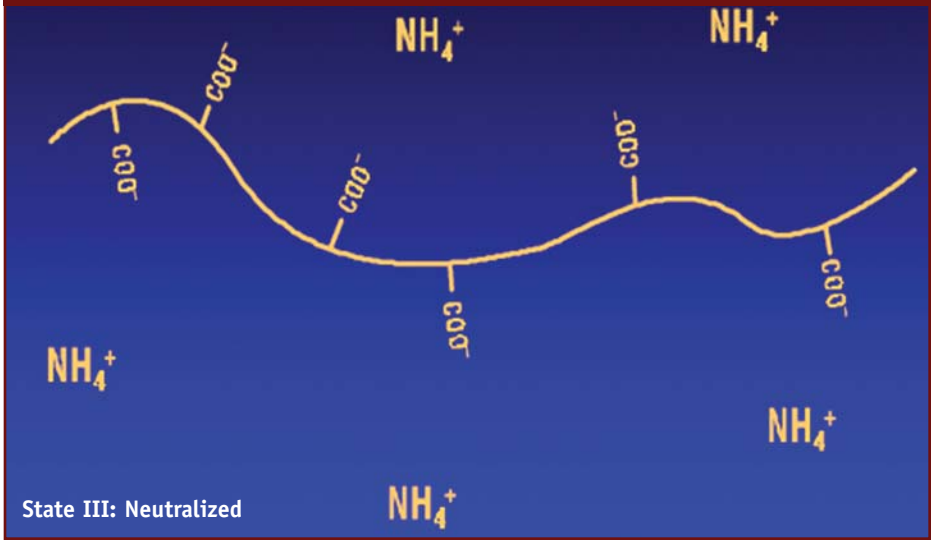

Table 3. Carbopol Market Applications

Personal Care	Pharmaceuticals
Shampoo	Controlled release in tablets and capsules
Styling Gel Hair /Dye / Color	Toothpaste and Oral Care
Nail Care	Bioadhesion in buccal, ophthalmic, intestinal, nasal, vaginal, and rectal applications
Creams and Lotions	Topical lotions, creams, gels, and transdermal systems.
Sunscreen	Suspending insoluble ingredients in oral suspensions, and topicals
Body Wash	Emulsifying topical oil-in-water systems

ingredients in transdermal reservoirs as well as in topical gels and creams. Controlled release could be achieved with a smaller amount of coating by using Carbopol as a coating material. A number of drugs have been formulated as controlled-release formulations using Carbopol as a matrix agent. Carbopol is a replacement for sodium CMC, all gums, xanthane gum, sodium alginate, poly-acrylic acids, etc. This multiple applications of Carbopol make it unique in the pharmaceutical field.

ACKNOWLEDGEMENT

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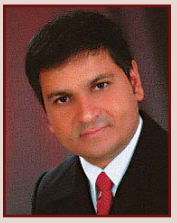

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PEPTIDE DELIVERY

Peptide Delivery Seeking to Become a Profitable Endeavor Through New Technologies

By: Jason McKinnie, Research Analyst, Frost & Sullivan

INTRODUCTION

Eliminating the needle in peptide delivery is proving to be one of the more daunting challenges in the drug delivery industry, but companies are making impressive headway in creating viable alternatives to painful and bothersome injections. The physical properties of peptides have often precluded it from alternate forms of delivery due to their size, proclivity for enzyme degradation, and lack of absorption. New technology and research is now providing opportunities to deliver peptides through alternative administration routes, such as pulmonary, oral, intranasal, and transdermal.

The field of peptide drug delivery took a tremendous step forward as a practical option with the approval of Exubera from Pfizer and Nektar Therapeutics. Insulin has long been a target of drug delivery companies due to the number of patients using it and the difficulty and issues surrounding the reliance on injections. Companies are confident that ease of use and elimination of the needle will be enough to counter the added cost of alternative protein delivery, and Exubera is expected to reinforce this notion. The approval of this drug has legitimized alternative forms of drug delivery, providing patients with increased hope of eliminating or reducing dependence on injections and instilling confidence to numerous drug delivery companies that alternative peptide delivery can win approval from federal regulators.

PULMONARY DELIVERY

The lungs provide an attractive target for both systemic and local drug delivery because of the large surface area and efficient uptake of pharmaceuticals. The immediate entry into the bloodstream offers several advantages for conditions that require rapid onset of activity. The difficulty lies in getting a formulation that is stable enough to be delivered via the lungs yet small enough to be properly absorbed. Pulmonary peptide delivery is proving especially difficult in manufacturing a formulation of the peptide that has the physical characteristics to be successfully absorbed in the lungs. Several companies are utilizing various techniques to make this feasible, with Exubera being the first product on the market. Most companies are targeting insulin with their technology, as it is one of the most common peptides utilized in treatment. Unlike drug development, companies develop a delivery technology that utilizes certain processes and then apply it to a particular drug.

Nektar Therapeutics developed a technology focused on stabilizing macromolecules for pulmonary delivery. Their dry powder formulation technology allows for a protein or macromolecule to be stabilized utilizing their proprietary glass stabilization technique. This process creates a macromolecule that is stable under room temperature conditions. The process also creates particles that range from 1 to 3 microns, ideal for quick lung absorption. Exubera was created utilizing these processes and is marketed to replace mealtime injections, and clinical trials have showed that the pulmonary delivery of insulin acts faster than insulin delivered through the skin. Patients that smoke are not expected to be treated with Exubera because their lungs absorb differently from non-smokers, making the dosages difficult to modify.

Alkermes and partner Eli Lilly are also utilizing proprietary technology to create a fine dry powder formulation for peptides to be delivered via the lungs. Their partnership is built upon the AIR technology platform that creates small, 5-micron sized particles to be delivered through a small, easy-to-use inhaler. This platform has resulted in inhaled insulin that is undergoing Phase III testing as a substitute for mealtime insulin

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"There has yet to be a blockbuster drug that utilizes alternative peptide delivery and that is why there is so much attention and pressure on Exubera to succeed in the market. To continue obtaining adequate funding for research and development of novel drug delivery mechanisms, substantial market success and profitability needs to be achieved."

injections. The AIR technology has also yielded two other products, including human growth hormone and parathyroid hormone. Human growth hormone is normally given to children, but that population has not been thoroughly studied with an inhaled peptide.

Aradigm is a drug delivery company focused on injectable and pulmonary formulations with an insulin product being their lead drug candidate for pulmonary delivery, currently in Phase III development. The company's AERx Pulmonary Delivery technology is centered on its device that can be modified based on the characteristics of the drug. A disposable dosage strip provides the drug and is delivered using a piston mechanism expelling the drug through a nozzle within the device. The use of a nozzle, approximately 1 micron in diameter, helps produce a particle that has a uniform size and shape. Unlike the Alkermes and Nektar Therapeutics inhalers, AERx uses a mechanical means to expel the drug.

INTRANASAL DELIVERY

Delivery in the sinuses is quickly expanding as a solution to delivering peptides systemically or to the central nervous system. One of the major advantages to this delivery method is that little reformulation has to be done to the individual drug that fits the profile for intranasal delivery. Unlike pulmonary drugs that require strict size limitations and special manufacturing practices, or oral delivery that requires some form of protection from enzyme degradation, intranasal delivery allows for quick and easy uptake of delivered molecules with little to no modification. Size of the particle is one limitation to intranasal delivery because they need to be larger than 10 microns or else they are more likely to be deposited into the lungs. Molecule size also is a limitation in intranasal delivery because larger molecules have difficulty being absorbed by the mucosal layer. It's widely accepted that 1000 daltons is the largest size a molecule can have for easy absorption without an added enhancer.

One of the earliest alternative peptide delivery drugs is Miacalcin from Novartis. This intranasal spray, launched in 1995, delivers a dose of salmon calcitonin for the treatment of osteoporosis. Patients typically take one spray daily and do not suffer some of the side effects associated with pills, such as irritation in the GI tract. Miacalcin is the third-line option for treatment of postmenopausal osteoporosis as hormone therapy and newer medications are currently favored. Unigene recently launched Fortical, an intranasal version of salmon calcitonin, in August 2005 with similar indications to Miacalcin.

Current research into the use of enhancers is enabling companies to allow for better absorption of larger peptides. Use of molecules called bioadhesive agents aid in the absorption of large proteins by allowing the molecules to remain in the nasal passages longer. Studies have shown bioavailability increases significantly with the use of an enhancer, especially for peptides that are longer than 20 amino acids. Nastech has developed a research program focusing on tight junction biology and has identified compounds that help open this pathway to deliver large macromolecules such as proteins. Through this technology, they have developed intranasal delivery options for a peptide related to obesity and parathyroid hormone; both projects are presently in Phase I.

Systemic delivery is already having success in the market place, but the most exciting development for intranasal drug delivery is the ability for drugs to cross the blood brain barrier (BBB). The BBB has caused tremendous difficulty in allowing for drugs to enter the central nervous system and treat the brain directly. Continued studies of the biology of the sinuses have revealed the ability to cross the BBB through olfactory nerves within the sinuses. Researchers have found in animal models it is possible to deliver proteins through the sinus and have the drugs enter the central nervous system within minutes. This revelation is now providing hope for new treatments relating to pain, Alzheimer's, and Parkinson's diseases.

TRANSDERMAL DELIVERY

Transdermal delivery offers a variety of advantages for drug delivery with sustained delivery being one of the most useful characteristics, especially for pain management and diseases that require constant treatment such as diabetes. Transferring a peptide across the skin is difficult and requires manipulation of the medicine to make it viable to enter the bloodstream as simple diffusion will not work for large peptides. While transdermal patches exist for many steroid hormones, peptide transdermal delivery is still in the early stages of development.

As one of the leaders in transdermal delivery, 3M has created a technology called Microstructured Transdermal System (MTS) that uses small needles that penetrate into the skin, but not deep enough to activate the nerves that feel pain. These structures allow for transfer of large macromolecules, up to 19,500 daltons, and it has been shown in laboratory settings that peptides can be delivered in this manner.

ORAL DELIVERY

The challenges of delivering peptides through the gastrointestinal tract are numerous and hard to combat. Large macromolecules are not readily absorbed through the epithelial cells of the GI tract, thereby limiting the efficacy of the drug. Peptides are also susceptible to degradation from enzymes in the GI tract that render the peptide inert. The oral route of drug administration is still the most preferred method because patients feel it's easier and tend to comply with their medications better. The overwhelming attractiveness of oral administration is prompting numerous companies to develop technology to overcome the challenges of oral peptide delivery. As a result, there is a high degree of innovation and competition with multiple products already in clinical trials.

Similar to pulmonary drug delivery, oral drug delivery companies develop a technology and then apply it to existing drugs. One of the

more diverse pipelines is from Emisphere Technologies. Their proprietary eligen technology platform is based upon synthetic carriers that allow a peptide to enter the bloodstream through the body's natural passive transcellular transport process in the GI tract. The carriers do not alter the conformation of the delivered drug but do alter the physical properties at the point of transport, not affecting the efficacy of the drug. Using this delivery platform, Emisphere Technologies is currently developing five peptides for oral delivery, including heparin, insulin, salmon calcitonin, hgh, and the weight-loss associated hormone PYY. The company is planning a Phase III clinical trial for their lead product oral heparin.

Nobex Corporation developed a process for adding an alkyl-PEG conjugate to peptides. This conjugate allows for more stabilization of the protein in the stomach and helps limit enzyme degradation. The properties of the alkyl-PEG also allow for the protein to be absorbed more easily by the GI tract through both hydrophilic and fatty components of the cells. The alkyl-PEG conjugate can also be modified to control the proteins' interaction in the bloodstream, allowing for longer duration of the drug in the body. Nobex used this platform to develop oral versions of insulin, calcitonin, and human brain-type natriuretic peptide (hBNP), a treatment for congestive heart failure. Oral insulin and nBNP are in Phase I clinical development. The company filed bankruptcy in December 2005, and its partner for many projects, Biocon, is attempting to buy the intellectual property of Nobex and continue development of these drugs.

SUMMARY

The peptide drug delivery industry has made significant progress in developing novel ways of delivering complex molecules without the use of needles. Patients want this technology if it can improve their quality of living, and physicians want this if it helps improve patient compliance. The technical challenges of delivering peptides are starting to be overcome but one more difficult challenge remains and that is to get patients and physicians to buy into these novel deliveries. Another challenge is ensuring new peptide drug delivery products are more efficacious than existing therapies. Miacalcin has suffered declining revenues in recent years due to more efficacious and orally delivered products, but that is typical of older products. There has yet to be a blockbuster drug that utilizes alternative peptide delivery and that is why there is so much attention and pressure on Exubera to succeed in the market. To continue obtaining adequate funding for research and development of novel drug delivery mechanisms, substantial market success and profitability needs to be achieved.

BIOGRAPHY

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

NON-INVASIVE INSULIN DELIVERY TECHNOLOGIES:

CURRENT TRENDS & FUTURE PROSPECTS

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

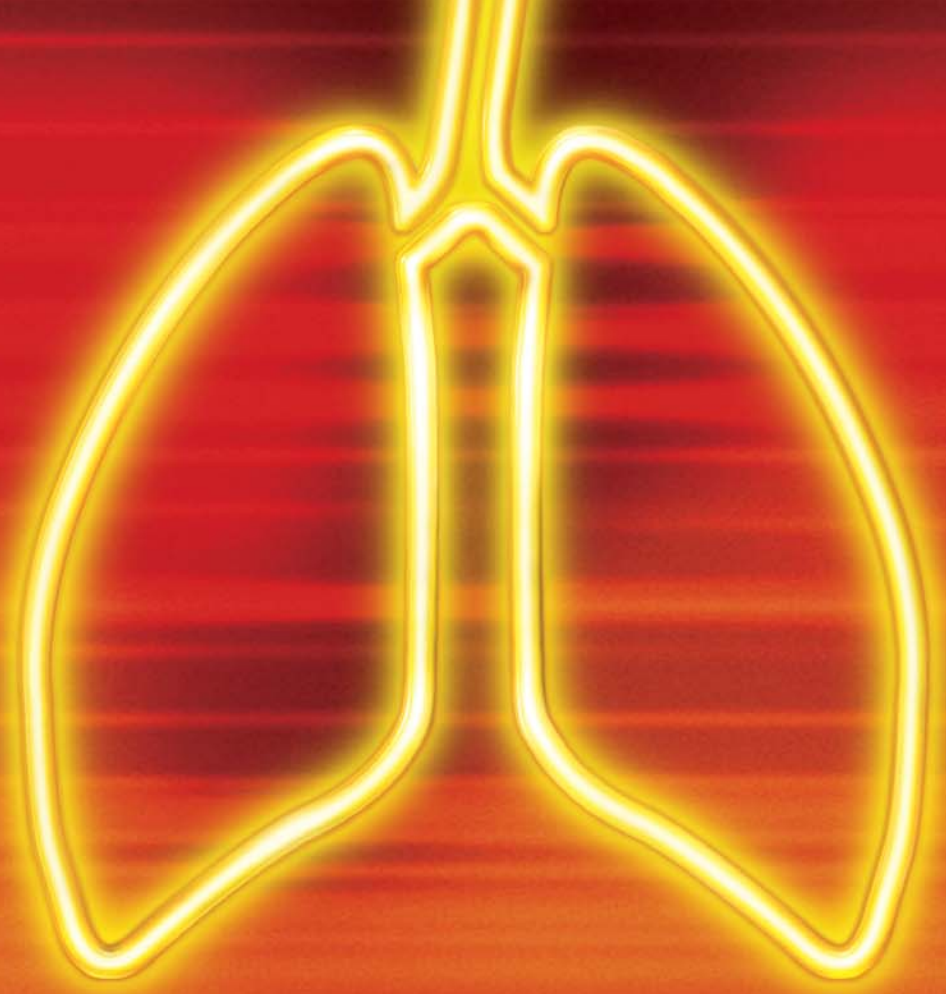
ABSTRACT

The introduction of insulin therapy 80 years ago has saved the lives of millions of patients with diabetes. Since then, there have been significant developments in the treatment of diabetes, especially with Pfizer's Exubera [insulin human (rDNA origin)] Inhalation Powder being approved by the US FDA for the treatment of adults with type 1 and type 2 diabetes. A rigorous research effort has been undertaken worldwide to replace the authentic subcutaneous route by a more accurate and non-invasive route. Considerable progress has been made to achieve new milestones for effective treatment of diabetes. Peroral, nasal, and pulmonary administration has demonstrated good potential for treatment of diabetes. In addition, transmucosal, buccal, ocular, rectal, and vaginal routes of insulin have also shown to decrease serum glucose concentrations. The transdermal route using various technologies also exhibits success in delivering insulin. This report presents a comprehensive review of the potential non-invasive technologies, the various insulin devices, and the major advancements in modern insulin delivery technologies.

INTRODUCTION

Diabetes mellitus is a group of metabolic diseases characterized by high blood sugar levels, which results from defects in insulin secretion or action, or both. Normally, blood glucose levels are tightly controlled by insulin, a naturally occurring hormone secreted from specialized cells (beta cells) of the pancreas. Glucose from the digested food is absorbed by the intestinal cells into the bloodstream and is carried by blood to all the cells in the body. However, glucose cannot enter the cells alone and needs insulin for its transport into the cells. In response to the increased glucose levels, the pancreas normally release insulin into the bloodstream to help glucose enter the cells and lower blood glucose levels. When the blood glucose levels are lowered, the release of insulin from the pancreas is turned off. In normal individuals, such a regulatory system exists to keep blood glucose levels in a tightly controlled range. In patients with diabetes mellitus, insulin is either missing (as in type I diabetes mellitus) or insulin is relatively insufficient to meet body's needs (as in type II diabetes mellitus). Both cause elevated levels of blood glucose (hyperglycemia). Without insulin, cells become starved of glucose. Elevated levels of blood glucose (hyperglycemia) lead to spillage of glucose into the urine. Over time, diabetes mellitus can lead to blindness, kidney failure, and nerve damage, and it is also an important factor in accelerating the hardening and narrowing of the blood vessels (atherosclerosis), leading to strokes, coronary heart diseases, and blood vessel diseases. By increasing the uptake of glucose by the cells and reducing the concentration of glucose in the blood, insulin prevents the long-term complications of diabetes.

The advent of insulin by Banting and Best in 1921 has revolutionized the treatment of diabetes and is one of the most outstanding achievements of 20th century medicine.[1] Throughout the past 75 years, subcutaneous injections have been the only route of delivery of insulin therapy to diabetic patients.[2] Despite the widespread use of conventional subcutaneous insulin injection, the process is more or less painful, inconvenient, and delivers insulin slowly with highly inconsistent pharmacokinetics as well as suboptimal pharmacodynamic properties. Even within



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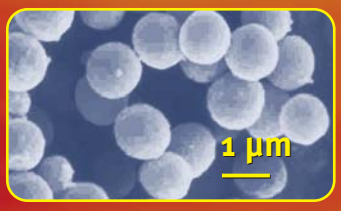

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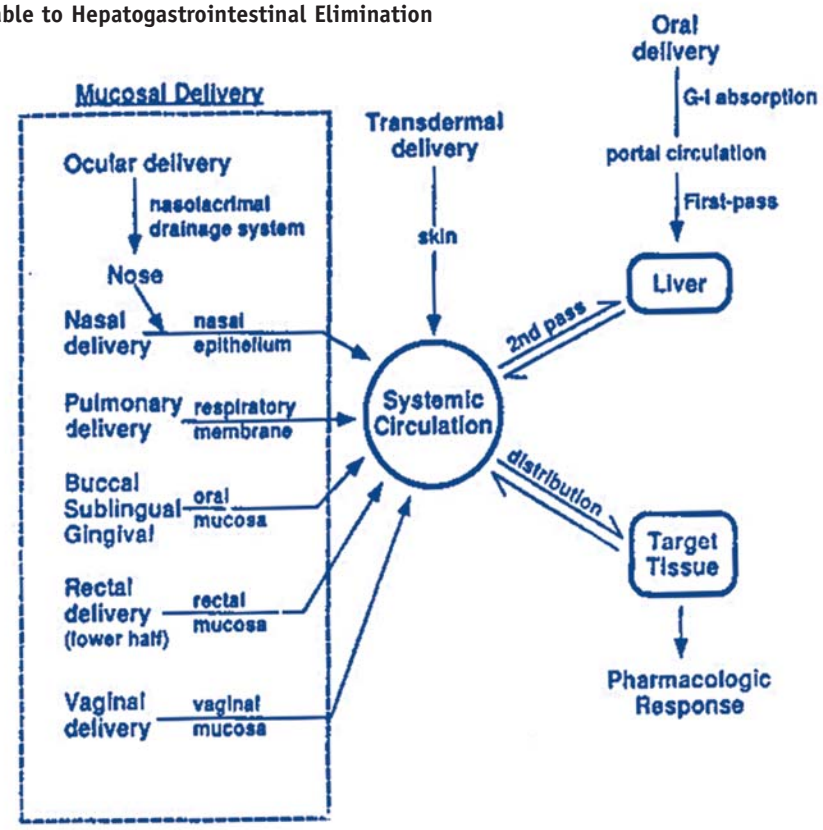
NON-INVASIVE INSULIN DELIVERY TECHNOLOGIES:
CURRENT TRENDS & FUTURE PROSPECTS

FIGURE 1

Alternative Routes for Systemic Delivery of Insulin Liable to Hepatogastrointestinal Elimination



an individual, there is a wide variation in the serum glucose concentrations for the same dose of insulin injected.[3] Due to extensive degradation of orally administered insulin by proteases in the gastrointestinal tract, insulin is currently ideally suited to be administered via the parenteral route (noting the recent Exubera inhalation powder approval).[4] However, the therapeutic goal of the treatment is to achieve a near normal metabolism as is practicable, ie, to achieve and sustain near normal glycemia. Not surprisingly, stable blood glucose concentrations are difficult to achieve, and the cost to the community by and large is enormous.

Therefore, implementation of insulin strategies to maintain long-term near normoglycemia (blood glucose 70 to 120 mg/dl) is of key importance in the management of diabetes mellitus. Owing to the major breakthroughs in the field of science and technology in the 21st century, success can be met in achieving this difficult goal. One of the two advances achieved to date in this direction are human insulin analogue synthesis with superior pharmacokinetics, which is produced by transpeptidation and biosynthesis in microorganisms. The other one is in the improved drug delivery systems that utilize noninvasive modes of administration.[5] Scientists have explored several attempts for alternative routes for systemic administration of insulin.[6,7]

Scientists have been actively researching other options for safe and effective insulin administration other than the parenteral route.[8,9] Figure 1 depicts the various alternative routes that are undergoing research and are liable to hepatogastrointestinal first-pass elimination. Attempts to develop alternative routes for administration began soon after its discovery, yet scientists have been able to achieve limited success. Several alternative, convenient, and novel routes have been investigated for insulin delivery to overcome the present long-term dependence on multiple subcutaneous injections.

The purpose of this review article is to highlight the current developments of non-invasive insulin drug delivery systems and discuss the trends of alternative routes of insulin delivery, such as oral, buccal, ocular, nasal, pulmonary, colon, vaginal, and transdermal. The present article reviews current trends and alternative possibilities of insulin delivery systems and emerging strategies to ensure the health and safety of millions of diabetics around the world.

ORAL DELIVERY

The oral gastrointestinal tract is the most preferred route of choice for most drugs. The administration of insulin orally would also be of great advantage, but insulin administered orally is degraded by the highly acidic gastric fluid in the stomach and by the proteolytic enzymes present in the small intestine and in presystemic metabolism. The epithelial surfaces of the gastrointestinal tract also pose a barrier to the absorption of this polypeptide. Other disadvantages are lack of selective insulin transport mechanisms across the gastrointestinal wall, stability of the protein, unpredicted transit time, and delayed absorption of the several attempts of formulation of oral insulin. The extent of absorption of intact insulin however is a major concern. However, in the past few decades, a great potential has been foreseen in the delivery of insulin by the oral route. If proven feasible, it would greatly boost patient compliance for insulin. Among the newer routes of administration explored, the oral appears to be the most physiologically convenient and appropriate. Scientists have adopted various approaches toward designing delivery systems for oral administration of insulin, but none have produced clinically satisfactory results.

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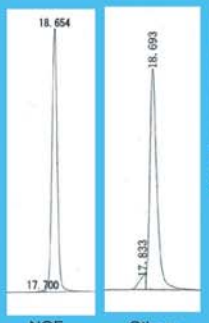

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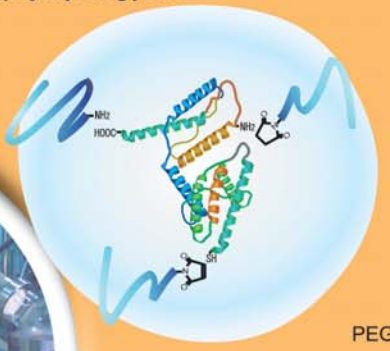

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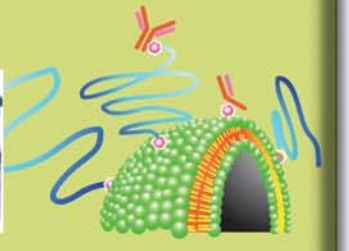

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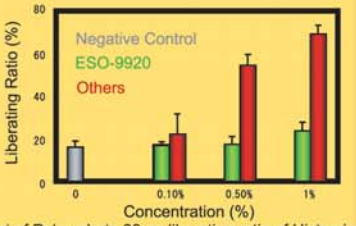

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NON-INVASIVE INSULIN DELIVERY TECHNOLOGIES:
CURRENT TRENDS & FUTURE PROSPECTS

FIGURE 2

Buccal Delivery: Oral-lyn™ Delivered Into the Mouth via RapidMist™ Device by Generex

Despite the use of various strategies, generally less than 1% to 2% of orally administered insulin is absorbed. Various approaches have been tried to overcome the cited drawbacks of orally administered insulin. Researchers have used insulin with protease enzyme inhibitors to slow the rate of degradation of insulin and an α-chymotrypsin-like pancreatic inhibitor, soybean trypsin inhibitor, FK-448, camostat mesylate, approtinin and bacitracin, and sodium glycolate.[10-13]

Permeation enhancers have also been employed to improve the absorption by increase in the paracellular and transcellular transport. Substances, such as bile salts and calcium chelators, and surfactants, such as sodium laurate, cetyl alcohol, and sodium cholate, have been utilized to increase the absorption of oral insulin.[14-17] Other methods that have been designed to improve the chemical stability of oral insulin are by the use of polymeric systems, mucobioadhesives, microspheres, liposomes, and emulsions.

Non-biodegradable and biodegradable biopolymers have also been used as such or in combination with absorption modifiers, such as enzyme inhibitors and permeation enhancers. The techniques of enteric coating and microencapsulation (18, 19) have been tried using polymers like Eudragit L100 and ES100, chitosan, alginates (20), azopolymer, and poly (vinyl alcohol) with approtinin and sodium cholate.[18-23]

Polymeric systems with inhibitors like duck ovomucoid and chicken ovomucoid have also been successful formulations for the oral delivery of insulin.[24-26] Carboxy methylcellulose polymer with inhibitor conjugates like Bowman Birk Inhibitor and Elastinal has demonstrated to offer *in vitro* protection against trypsin, chymotrypsin, and elastase. They demonstrated up to a 40% reduction in basal glucose levels. Proteolytic enzymes chymotrypsin and trypsin can degrade insulin. Insulin with carbopol polymers at 1% to 4% w/v was also able to reduce proteolysis by shifting intestinal pH away from optimal pH for proteolytic degradation.

Microspheres & Nanospheres

Non-biodegradable and biodegradable polymers have been used to prepare microspheres and nanospheres for oral delivery of insulin. Non-biodegradable polymers, such as Isobutyl-2-cyanoacry late, poly (alkyl cyanoacrylate) that directly administers into the intestine and colon, have also been developed.[27]

Biodegradable microspheres of poly (fumaric anhydride) and poly (lactide-coglycolide) have also been prepared.[28] Natural biocompatible polymers like chitosan and alginates have also been used as coating polymers along with absorption enhancers and protease inhibitors.[20] Musabayane and co-workers have entrapped insulin in amidated pectin hydrogel beads.[29] Beads and microspheres of insulin have also been prepared using poly-L-lactide.[30] Oral administration of insulin encapsulated in biocompatible self-assembled nanocubicles also reduced blood glucose levels in animals.[31]

Liposomes

Scientists have highlighted the feasibility of systemic insulin delivery by the oral route using liposomes and reported that a substantial blood glucose reduction was observed in diabetic animals.[32] The reduction in blood glucose levels from liposomes depends on factors like amount and type of lipid used, size and surface charge, and physicochemical characters of liposomes.[33-35] Conventional liposomes are susceptible to enzymatic degradation and bile salt dissolution, thus they are made resistant to gastrointestinal tract environment by polymerization and pegylation techniques.

The feasibility of using liposomes as a potential oral delivery system for the systemic delivery of insulin has been extensively studied.[36] Liposomes prepared from phosphatidyl choline and cholesterol significantly reduced the blood glucose levels in diabetic rats.[37]

Ramdas et al developed an oral formulation for insulin delivery based on liposome-encapsulated alginate-chitosan gel capsules with high entrapment efficiency and was successful in reduction of blood glucose levels in rats.[38]

Liposomes of insulin prepared by Moufti and coworkers and Patel et al could produce a 50% reduction in blood glucose levels.[39,40] Another strategy used to improve the absorption of orally administered insulin includes modification of the insulin by the covalent attachment of one or more low molecular weight amphilic oligomers. This modification increases solubility and stability. An attempt in this category is the preparation of encapsulated hexyl-insulin monoconjugate-2, which could cause reduction in blood glucose levels.[41] Another trial includes use of non-acylated amino acids.[42]

A number of pharmaceutical companies have commercially investigated the use of oral insulin and developed technologies to improve its bioavailability. A summary of the commercially developed insulin formulations and technologies for oral insulin are summarized in Table 1.[43,44]

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NON-INVASIVE INSULIN DELIVERY TECHNOLOGIES:

CURRENT TRENDS & FUTURE PROSPECTS

Table 1. Commercially developed insulin technologies through oral route.

NAME OF COMPANY/RESEARCHER	TECHNOLOGY
Ariad Pharmaceutical	RAPID™, Regulated Accumulation of Proteins for Immediate Delivery
Autoimmune/Eli Lilly	AI-401, oral agent
Cortecs	Macrulin, Phase I clinical trials
Elan	Oral form, Phase I clinical trials
Emisphere Technology, Inc.	Oral capsule using non-acylated amino acids as carriers
Endorex Corp.	Orasome technology, encapsulation of insulin in liposomes
Nobex Corporation	M2 oral product, low molecular weight polymer conjugated system, Phase III trials
Professor Ferrari	Oral MEDDS (Micro-Engineered Drug Delivery System), microfabricated particles
Unigene Laboratories Inc.	Insulin capsule

TRANSMUCOSAL DELIVERY

Mucoadhesive polymers have received considerable attention for controlling the peroral delivery of insulin. These polymers are an important class of compounds, and they help in prolonging residence time at the site of drug absorption, increase the contact with the absorptive mucosa, and help to improve and enhance the bioavailability. Polymers, such as poly (acrylates), chitosans, poly(glucan) derivatives, and hyalouran derivatives, have been extensively researched. These polymers are multifunctional macromolecules and are able to increase the permeability of epithelial tissues and simultaneously inhibit proteolytic enzymes. The mucoadhesive polymers coupled with various strategies to improve the transmucosal absorption of insulin has been used extensively by scientists and is compiled in Table 2.[45] Mathiowitz et al have developed insulin containing poly (anhydride) microspheres, which adhered to the walls of the small intestine and released insulin based on the degradation of the polymeric carrier.[46] Nakamura et al developed a bioadhesive, complexation hydrogel system for oral delivery of insulin. This device consists of insulin containing microparticles of cross-linked graft copolymers of polymethacrylic acid and polyethylene glycol (P(MAA-g-EG).[47]

BUCCAL DELIVERY

The buccal mucosal is more permeable than skin, provides a large surface area for absorption, and is a desirable site for sustained release. This delivery system offers many advantages, such as improved patient compliance due to accessibility of cheek lining and no invasive measures needed. Insulin can enter directly into the systemic circulation, thereby avoiding enzymatic degradation in the gastrointestinal tract, little proteolytic activity, and first-pass metabolism in liver. The high molecular weight insulin can easily permeate through buccal tissues as compared to intestinal permeation. Dosage forms, such as gels, films, and patches, have been reported to reduce blood glucose levels in animals.

Ishida et al developed an oral dosage from for insulin consisting of a coating of hydroxypropyl cellulose and carbopol.[48] Studies of insulin tablets using similar polymers were also performed by Nagai et al.[49] Bile salts and surfactants have been used as penetration enhancers to increase the absorption of insulin. In this category, sodium cholate, sodium taurocholate, sodium lauryl sulphate, and Brij 35 have also demonstrated to increase the bioavailability of insulin. A bucco-adhesive delivery system of insulin was developed by Nagai and Machida.[50] They concluded that the formulation composition significantly affected the delivery of insulin. Buccal absorption of insulin could be achieved using a dome-shaped, two-phase mucosal adhesive device containing insulin with an absorption promoter, such as sodium glycocholate, and polymers, such as hydroxypropyl cellulose and carbopol 934.[51] Other strategies via the buccal route include addition of enzyme inhibitors, molecular modification to increase the lipophilicity of insulin, such as conjugation, acylation, methylation, and use of prodrugs.[52-54]

Generex Biotechnologies has developed a liquid formulation of insulin in the form of a spray Metered Dose Inhaler to be sprayed in the mouth. The rapid absorption via the mucosal lining was successful in the reduction of blood glucose levels.[55] The

NON-INVASIVE INSULIN DELIVERY TECHNOLOGIES:
CURRENT TRENDS & FUTURE PROSPECTS

FIGURE 3

Pfizer's Exubera [insulin human (rDNA origin)] Inhalation Powder Recently Approved by the US FDA for the Treatment of Adults With Type 1 & Type 2 Diabetes

device known as RapidMist™ is in Phase II clinical trials (Figure 2). The same company has also developed ORALGEN. DelRx, a New Jersey company, has also successfully developed a unique novel dosage form for insulin for buccal administration.

NASAL DELIVERY

The administration of insulin via the nasal route is another extensively researched alternative for administration of insulin. This route provides a large surface area, porous endothelial membrane, high total blood flow, bypass of first-pass metabolism, and ready accessibility. Drugs are cleared rapidly from the nasal cavity following intranasal administration, resulting in rapid systemic absorption. Several approaches have been utilized by various scientists for improving the nasal absorption of insulin. The concept of bioadhesion is the most preferred, and dosage forms, such as microspheres, liposomes, gels, liquid formulations, self-gelling systems, and bioadhesive powders have been utilized. The transdermal permeability and nasal absorption of insulin were found to be enhanced by the coadministration of absorption promoters, such as bile salts, naturally occurring surfactants, synthetic surfactants, and recently, sodium taurodihydrofusidate, which has also shown to be an excellent absorption promoter for increasing the intransnasal permeation of insulin.[56] The systemic delivery of insulin by intranasal administration has been extensively studied by researchers.[57-61] The use of absorption promoters proved to be effective in delivering insulin via the nasal route. Gordon et al reported that sodium desoxycholate was most effective in increasing the nasal absorption of insulin. Nagai et al reported the use of an adhesive powder dosage form and powder spray for delivery of insulin. The powder form was more effective and less irritating than liquid forms. The powder form was prepared using hydroxypropyl cellulose as a bioadhesive base.[62] Bjorn and Edman investigated a nasal delivery system for insulin using degradable starch microspheres. Blood glucose was reduced upto 64%.[63]

Despite the advancements in the development of nasal insulin, it is associated with problems and thus requires proper investigation. The use of absorption enhancers to increase the bioavailability of nasal insulin causes irritation to the nasal mucosa and has certain side effects. The long-term safety of these enhancers is also of great concern. There are also chances of intra and interindividual variability in bioavailability due to the difference in clearance mechanisms and variable mucous production. The anatomic structure of the nose also affects the delivery. Inspite of these problems, a large number of nasal inhalers for insulin are being studied.

Bentley Pharmaceuticals, Inc., carried out preclinical evaluation studies for intranasal formulations, and the company has achieved promising results. Similar studies on nasal delivery of insulin have been undertaken by Vectura Ltd. and ML Laboratories. West Pharmaceutical Services have used chitosan as an absorption enhancer in nasal delivery of insulin.

PULMONARY DELIVERY

The pulmonary route is a promising alternative route for the delivery of insulin, especially with Pfizer's Exubera [insulin human (rDNA origin)] Inhalation Powder being approved by the US FDA for the treatment of adults with type 1 and type 2 diabetes (Figure 3). Through this mode of administration, insulin is deposited in the lungs by oral inhalation and is absorbed through the lung mucosa into the systemic circulation. It offers the following several advantages:

- Non-invasive Route
- Large Surface Area
- Good Vascularization
- Immense Capacity for Solute Exchange
- Ultra-thickness of the Alveolar Epithelium
- Absence of Certain Peptidases That are Present in GI Tract
- Marginal Variance in the Amount of Mucus Production

The pulmonary delivery of insulin has made good progress and this has attracted the attention of pharma and biotech companies worldwide.[64-66] Several investigators have shown that this intrapulmonary delivery if insulin lowers plasma glucose in various animal and human studies.[67,68] Insulin, when administered as an aerosol formulation and delivered by a nebulizer, achieved up to 16% absorption in diabetic patients.[69] Use of absorption promoters, such as azone, fusidic acid, and glycerol increased the absorption of insulin in rats.[70] In another clinical study on diabetic patients, insulin-containing aerosol generated by a Raindrop nebulizer achieved about 80% deposition of inhaled insulin. Also, insulin poly (lactic glycolic) acid

NON-INVASIVE INSULIN DELIVERY TECHNOLOGIES:
CURRENT TRENDS & FUTURE PROSPECTS

Table 2. Strategies for improving transmucosal delivery of insulin.

STRATEGY	METHOD
Absorption Enhancers	crown ethers, β-Cyclodextrin derivatives, salicylate MCC dispersions with hydroxypropyl cellulose
Enzyme Inhibitors	bestatin, aprotinin, soyabean trypsin inhibitor, aprotinin, bacitracin, camostat mesilate, sodium glycocholate microcapsules, nanocapsules, nanoparticles,
Carrier Systems	emulsion (water-in-oil-water), liposomes, biomembranes of erythrocytes, polyacrylic polymer-coated soft gelatin capsules, azopolymer coated hard gelatin capsules

nanospheres delivered through a nebulizer in guinea pigs caused significant blood glucose reduction.

One of the major challenges in the pulmonary delivery of drugs is to achieve reproducibility at the deposition site of the applied dose. The rate of absorption of the drug depends on the variation of thickness of the epithelial lining and other anatomic and physiological variables. The aerosol requires generating droplets of size in a monodisperse distribution for effective transfer. Only particles with a size of less than 10 µm are transported into finer bronchial branches and alveoli. However, particles with a size of less than 1 µm are also not deposited on the mucous membranes but are exhaled. The optimal particle size for pulmonary insulin administration is in the range of 2 to 5 µm. A monodisperse aerosol with a mass median aerodynamic diameter of 3 µm was reported to achieve an alveolar deposition of insulin to be 50% or higher.

Metered dose Inhalers, nebulizers, and dry-powder inhalers are available to deliver insulin via the pulmonary route.[71] A summary of the pulmonary insulin devices provided through different technologies is shown in Table 3.[72]

COLON DELIVERY

Hydrogel-based controlled-release systems that can swell in the presence of biological fluid have been developed for the colonic delivery of insulin. Tonitou and Rubinstein have designed a colon-specific type of reservoir system wherein insulin was encapsulated by a polyacrylate gel.16 Saffran and coworkers developed another type of colon-specific insulin drug delivery, which was also a biodegradable hydrogel. The device consisted of insulin dispersed in a terpolymer of styrene and poly (2-hydroxyethyl methacrylate) cross-linked with a difunctional azo-containing compound.[73] A novel approach involves coating iodine with azoaromatic groups and subsequent cross-linking of azopolymers that form an impervious film, which protects the insulin from degradation in the gastrointestinal tract, and insulin is released in the colonic region.

RECTAL DELIVERY

The rectal route in the form of suppositories is one of the oldest routes and offers several advantages for delivery of insulin as compared to enteral routes. The following advantages include:

- Independent of intestinal motility, gastric emptying, and presence of food;
- Less amount of degradation enzymes in rectum as compared to proximal part of gastrointestinal tract;
- Avoidance of hepatic first-pass metabolism; and
- Improved bioavailability.

Researchers have carried out studies on the rectal delivery of insulin with and without adjuvants.[74,75] The coadministration of an absorption-promoting adjuvant, such as sodium glycocholate, enhanced the rectal absorption of insulin. A microenema of insulin when coadministered with sodium 5-methoxysalicylate significantly improved the rectal administration.[76] Phenylglycine enamines of β-diketones, such as ethyl acetoacetate, also improved the rectal absorption of insulin.[77]

OCULAR DELIVERY

The ocular route has also been used for the systemic delivery of insulin. Chriastie and Hanzel first studied this route in 1931 and reported the dose-dependent reduction in blood glucose levels following ocular administration of insulin in rabbits.[78]

The development of ocular drug delivery is always a challenge to the formulator due to the presence of local irritants loss in drainage, blinking, and tearing. The potential route to the anterior segment of the eye is the conjunctival cul-de-sac. Insulin is instilled into the precorneal cavity to reach the systemic circulation through blood vessels underlying the conjunctival mucosa or by overflow of the solution into the nasolacrimal drainage

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CURRENT TRENDS & FUTURE PROSPECTS

FIGURE 4A

Transdermal Insulin Technologies
A: SonoPrep Skin Permeation Device by Sontra Medical Corporation

FIGURE 4B

Transdermal Insulin Technologies
B: Programmable Ultrasonic Drug Delivery via Transdermal Patches (The U-STRIP™ by Dermisonics)

system. Ocular insulin was given as eye drops to anesthetized and awake rabbits.[79] The systemic bioavailability of insulin was also improved to 4% to 13% with the use of absorption promoters, such as bile salts, and non-ionic surfactants and permeation enhancers.

Various approaches that been investigated to overcome these drawbacks and which have been successful to an extent include use of polymeric systems, nanoparticles, liposomes, ocular inserts, and gels.[80-81] Practically, the route has many advantages, and one of the most important is termination of drug therapy when desirable. However, patients need to be explained the safety and feasibility of the route.

Lee et al have studied ocular inserts for insulin, and they have reported a significant blood glucose reduction.[82,83] BioSante Pharmaceuticals (Lincolnshire, Illinois) has developed Bio-Air™, which consists of calcium phosphate nanoparticles to improve delivery of insulin into the eyes.

VAGINAL/UTERINE DELIVERY

The vaginal route has been utilized for several decades for administration of therapeutic agents because it offers the following several advantages:

- Self-administration;
- Possibility of prolonged retention;
- Potential of avoidance of first-pass elimination; and
- Minimization of proteolytic degradation.

Fischer et al first studied the vaginal absorption of insulin and reported the observation of a rapid and temporary reduction in blood glucose levels in dogs and cats.[84]

Later, a formulation containing non-ionic surfactant polyethylene glycol demonstrated a reduction in blood glucose levels, but it was lower as compared to the rectal route.[85] Morimoto et al have prepared a vaginal formulation of insulin suspension in a polyacrylic acid aqueous gel base, and the formulation produced a rapid and pronounced hypoglycemic effect in rats and rabbits.[86] Microspheres of a novel class of biocompatible and bioadhesive polymers, known as HYAFF polymers, which are chemical modifications of hyaluronic acid and have been used to deliver insulin through the vaginal route.[87]

TRANSDERMAL DELIVERY

The human skin is an extremely thick barrier, so it is difficult to transfer proteins as large as insulin. However, because of lack of degrading enzymes, it is a good alternative route. In early experiments, a significantly less amount of insulin was delivered by this route because of its poor permeability and large molecular size.[88] Different techniques to increase the penetration of insulin through the skin, such as the use of chemical enhancers, iontophoresis techniques, electroporation, and sonophoresis and phonoporesis have

NON-INVASIVE INSULIN DELIVERY TECHNOLOGIES:
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Table 3. Commercially investigated pulmonary devices and technology for insulin.

NAME OF COMPANY	BRAND NAME	TECHNOLOGY
AeroGen Inc.,	Aerodose	Insulin Inhaler
Alkermes	AIR	Porous drug particle aerosol technology for fast and slow acting insulin from a capsule
Aradigm Corporation	AERx	Piston mechanism to expel insulin powder formulation from AERx strip, Phase III
Cambridge, Massachusetts, USA	Technosphere	Ordered Lattus array of Technosphere and human Insulin
Dura Pharmaceuticals	Apiros Blisterdisk	Inhaler
Epic Therapeutics	EPIC PROMAXX	Insulin microspheres of 1-2 µm in non-CFC propellants like hydrofluroalkane
ImaRx Therapeutics	PulmoRx	Inhaler with microbubble based carriers
Pfizer	Exubera	[insulin human (rDNA origin)] Inhalation Powder US FDA Approved

Table 4. Transdermal technologies for insulin.

COMPANY	TECHNIQUE	STUDY CONDUCTED IN
Altea Dev. Corporation	MicroPor (Needless Injections)	Animals
Cygnus Pharmaceuticals	Electroporation	Animals
Encapsulation Systems	Sonophoresis	Human Trials
Helix BioPharmac Corporation	BIPHASIX Microencapsulation in a patch	Rats
IDEA	Transfersulin	Phase I clinical trial
ImaRx Therapeutics	SonoRelease (Ultrasound-mediated)	????????????
Sontra Medical	SonaPrep (Ultrasound-mediated)	Pigs
Vector Medical Technologies Inc.	Transdermal Insulin patch	Completion of clinical trials

NON-INVASIVE INSULIN DELIVERY TECHNOLOGIES:
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been tried by various researchers and is reviewed in Table 4.[89,90] A technology known as innosonic (SonoPrep/Sontra Medica and U-STRIP/Dermisonics devices) combines iontophoresis and ultrasound for transdermal delivery of insulin (Figure 4). Another innovative approach is to increase the transport of insulin through the skin by use of transferosomes technology.[91,92] Transferosomes are particles similar to liposomes with more flexibility. Another new technique is the use of transfersulin whereby insulin was incorporated into vesicles of lipid particles.

Siddiqui et al used the Phoreser system, a dc iontophoretic device that could reduce blood glucose levels in rats.[93] A body-wearable dc iontophoretic delivery device called the Power-Patch applicator was also developed and tested in diabetic rats, and it was able to successfully transdermally deliver insulin through the negative reservoir electrode in rabbits. Iontophoresis-facilitated transdermal delivery of insulin is more efficiently accomplished by pulsed dc iontophoresis than by conventional dc iontophoresis.

SUMMARY

There is a long history of attempts to develop novel routes of insulin delivery that are both clinically effective and tolerable. The various approaches that have been studied have involved strategies that are designed to overcome the inherent barriers that exist for insulin uptake across the gastrointestinal tract, skin, and nasal mucosa. The advanced methods of insulin delivery systems would gradually progress toward physiological insulin replacement and reduce the long-term complications of diabetes mellitus. Thus, a feasible alternative route for insulin delivery is likely to emerge in the future. This new millennium promises a revolutionary change in the delivery of insulin, which is not too far off for billions of sufferers who are reliant on subcutaneous administration.

REFERENCES

References available from Drug Delivery Technology upon request.

BIOGRAPHIES

Dr. Avani F. Amin is currently working as an Assistant Professor in Pharmaceutics, Nirma University of Science & Technology. Dr. Amin has 5 years of regular teaching, 6 years as a visiting faculty and research scientist, and 2 years of industrial experience. She has more than 25 research publications in international and national pharmaceutical journals. She has also presented papers at various conferences. Dr. Amin is the recipient of the Motan Devi Dandiya Prize in Pharmacy, the Prof. M. L. Khurana Memorial Prize in Pharmaceutics, the G. P. Nair IDMA award, and other state level prizes. She earned her MPharm and PhD in Pharmaceutics.

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SUSTAINED RELEASE

Comparison of Acrylic & Cellulose-Based Matrix Formers for Sustained Drug Release

By: Diego Gallardo Álvarez

INTRODUCTION

Sustained drug release improves patient compliance, especially when used in long-term treatment. It is often achieved with matrix structures that may be obtained through processes like direct compression, roller compaction, wet granulation (high-shear mixer or fluidized bed) or melt technologies.[1] The chosen matrix formers, hydrophilic or inert polymers or combinations of both, should offer convincing properties both in terms of application and economy. The main mechanisms to release a drug from a matrix structure are swelling, gel diffusion, and erosion (hydrophilic polymers), as well as diffusion and pore diffusion (inert polymers).[2] The aim of this study was to compare EUDRAGIT® NE 30 D with Aquacoat® ECD and several Methocel® polymers as matrix formers along the different steps of the manufacturing process. The investigations focused on the suspension properties, the granulation process, compressibility, and release profiles as important parameters for comparison.

MATERIALS

The following materials were used to prepare matrix tablets: Diltiazem HCl (d50:12.5 µm) (lot # DIL 1504 and DIL 2101) was supplied by Lusochimica, Lomagna, Italy. Emcompress® (lot # E22D) was supplied by JRS Pharma, Rossenberg, Germany. EUDRAGIT® NE 30 D (lot # B040412009) was supplied by Roehm GmbH & Co. KG, Darmstadt, Germany. Methocel® E5 (lot # QG05012402), K4M (lot # KD18012N11) and K15M (lot # SA01012N12) were supplied by Colorcon Ltd., Michigan, USA. Aquacoat® ECD (lot # J3211) was supplied by Interorgana GmbH & Co. KG, Koeln, Germany. Pigment SICOVIT® E 172 (lot # 24782) was supplied by Th. Geyer GmbH & Co. KG, Renningen, Germany. Magnesium Stearate (lot # K-29292963) was supplied by Merck, Darmstadt, Germany.

The matrix formers studied were EUDRAGIT® NE 30 D and Aquacoat® ECD (as inert matrix formers) as well as several hydrophilic Methocel® polymers (most commonly used in the manufacturing of sustained-release tablets). From hydroxypropyl methyl cellulose polymers, three were chosen based on the differences in viscosity values. These differences in viscosity are responsible for the degree of retardation. The hydroxypropyl methyl cellulose polymers chosen covered a wide range of viscosity in order to see the influence on the retardation effect of the matrix tablets. The viscosity is related to the number average molecular weight (MN) of the different hydroxypropyl methyl celullose types. This number represents the average weight of the monomers forming the polymer chain. There is a correlation between viscosity values and MN.[3] Diltiazem HCl was used as a highly water-soluble model substance.

METHODS

Preparing the Granulation Suspensions

To prepare the EUDRAGIT® and Aquacoat® ECD spray suspensions, the commercial dispersions were diluted with purified water. All the suspensions were prepared at 20% polymer content.

The Methocel® solutions were prepared by first dispersing the polymer powder in 60°C purified water. Afterward, the dispersion was cooled down to room temperature with continuous stirring while forming a colloidal solution. Stirring was continued until the spraying process was completed. The polymer concentration in the solution depended on the viscosity of the different Methocel® grades. 500 mPa·s was considered as the maximum acceptable viscosity in order to ensure sprayability. In the case of Methocel® E5, the entire polymer quantity was dissolved, providing a 20% solution. For Methocel® K15M and

TABLE 1

Correlation between the viscosity and the MN values for the HPMC polymers.[4]

Polymers	Viscosity Grade 2%, 20°C, mPa·s	Number Average Molecular Weight (M_N)
Methocel® E5	5	10,000
Methocel® K4M	4,000	86,000
Methocel® K15M	15,000	120,000

TABLE 2

Polymer content and viscosity of granulation suspensions, granulation spray rates, polymer content, and LOD.

Polymer	Content in Suspension (w/w)	Granulation Spray Rates (l/h)	Content in Granules (w/w)	LOD (%)
Aquacoat® ECD	20.00	1.6	20	4.51
Methocel® E5	20.00	1.4	20	5.26
Methocel® K4M	1.14	1.2	20	5.18
Methocel® K15M	0.71	1.2	20	4.19
EUDRAGIT® NE 30 D	20.00	1.6	20	6.55

TABLE 3

Polymer content and viscosity of granulation suspensions

Polymer	Content in Suspension (w/w)	Viscosity (mPa·s)
Aquacoat® ECD	20.00	4.5
Methocel® E5	20.00	230
Methocel® K4M	1.14	345
Methocel® K15M	0.71	214
EUDRAGIT® NE 30 D	20.00	2.2

K4M, only a small percentage (0.71% and 1.14%, respectively) could be dissolved in order to keep the viscosity below 500 mPa·s and furthermore to keep the suspension volume on the same level as for the other granulation formulations. The remaining polymer quantity was added to the powder mixture in the fluidized bed, which consisted of the drug (Diltiazem HCl) and Emcompress® as binder. For every granulation liquid, 1% of iron oxide pigment was added.

Granulation Process

First Diltiazem HCl, Emcompress®, and if necessary, Methocel® powder were blended. Granulation was performed in fluidized bed, granulating the powder mixture with the granulation suspensions. A Glatt WSG-2 (top spray mode, Glatt AG, Binzen, Germany) was used as the fluidized bed equipment. The nozzle diameter was 1.2 mm, and the atomizing air pressure was 2 bar, except for the high-viscosity Methocel® solutions, which required 3 bar, in order to achieve small droplet sizes. The spraying process started at product temperatures of 25°C to 30°C (when EUDRAGIT® NE 30 D or Aquacoat® ECD were sprayed), or 30°C to 35°C (when the HPMC suspensions were applied). After the granulation process, the granules were dried in the fluidized bed for 5 minutes followed by drying in an oven at 40°C for 2 hours. The loss on drying (LOD) of the granules was determined using a Sartorius MA 30 / Moisture Analyzer, Goettingen, Germany.

Tablet Preparation & Characterization

The granules were mixed with magnesium stearate for 10 minutes in an ERWEKA bicone blender (ERWEKA GmbH, Heusenstamm, Germany) with a rotation speed of 25 rpm. Compression was performed on a Korsch EK0 (Korsch, Berlin, Germany) instrumented eccentric press (punch diameter 12 mm, curvature radius 20 mm) at different compression forces (5kN, 10kN, 15kN, 20kN, 25kN). An ERWEKA Multicheck (ERWEKA GmbH, Heusenstamm, Germany) was used to test the weight, height, diameter, and hardness of the tablets. The friability was determined using a PTF E (Pharma Test Apparatebau GmbH, Hainburg, Germany). These properties were determined for all tablet batches according to the European Pharmacopeia methods.

Drug Release

The dissolution test was performed with an ERWEKA DT 6, USP Apparatus II, (ERWEKA GmbH, Heusenstamm, Germany) connected to an UV/Vis Perkin-Elmer Lambda 20 (Perkin-Elmer GmbH, Uberlingen, Germany). Experiments were performed for 8 hours at two different pH values: pH = 1.0 (USP 28 0.1 N HCl) and pH = 6.8 (USP 28 potassium phosphate buffer). The temperature was 37°C ± 0.5 ºC, rotation speed 50 rpm,

FIGURE 1

Release Profiles at pH 1.0, 15 kN Compression Force

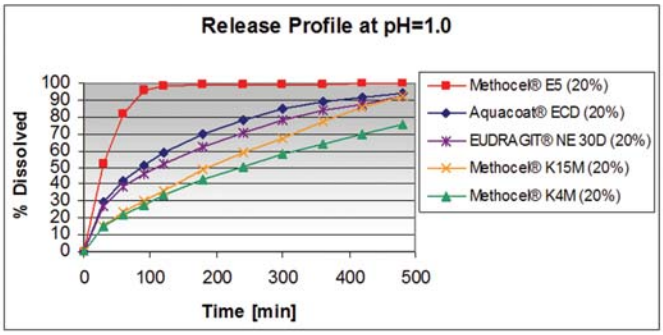
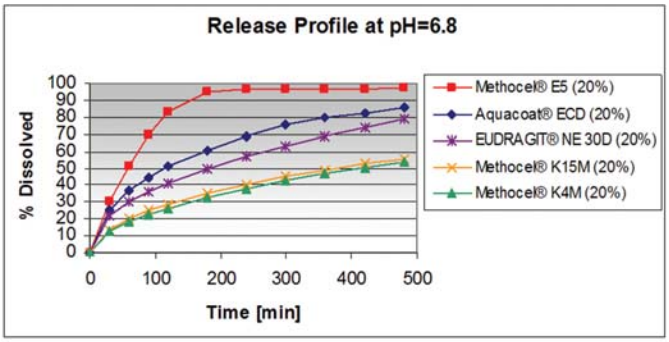


FIGURE 2

Release Profiles at pH 6.8, 15 kN Compression Force



volume 900 ml (samples having passed through a 10-_m filter). At the end, the samples were homogenized with an Ultra Turrax T45 (IKA® Werke GmbH & Co. KG, Staufen Germany).

For SEM characterization of the matrix structures, after the dissolution test was completed, the tablets were frozen with liquid nitrogen. Afterward, the residual moisture was dried out by applying a vacuum (5 ·10-5 mbar) for 2 hours. Sample preparation was performed by sputtering with gold using a "Cool" sputter coater, E 5100, Bio-Rad, Cambridge, USA. SEM was performed using a JEOL, JSM-840A, (Eching, Germany).

RESULTS & DISCUSSION

Granulation

The fluidized bed process was chosen as the application process because it leads to better distribution of the polymer and therefore a better retardation effect can be expected.[4]

EUDRAGIT® NE 30 D and Aquacoat® ECD suspensions showed much lower viscosity than the hydroxypropyl methyl cellulose preparations (Table 3). Colloidal solutions are characterized by higher viscosity caused by solved polymers, as compared with polymer dispersions, where the particles are suspended and thus do not impact the viscosity. The lower viscosity of the aqueous polymer dispersions results in easier suspension preparation and easier application.

Drug Release

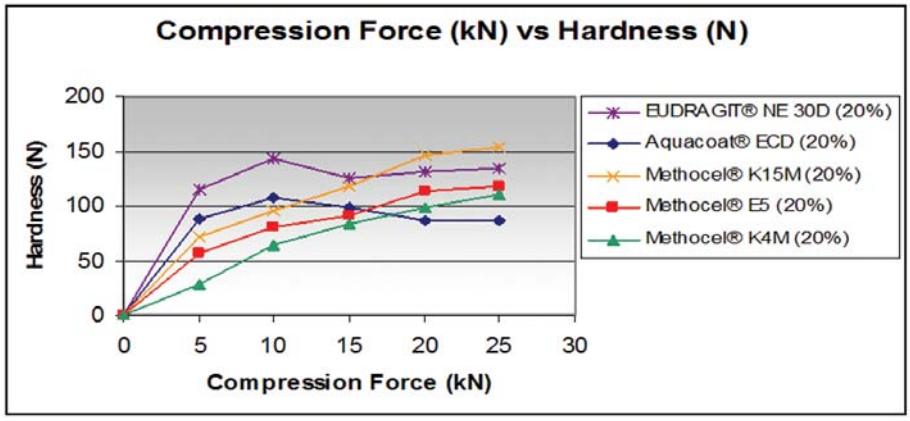
The release profile of the matrix tablets manufactured with hydroxypropyl methyl cellulose is governed by the viscosity of the hydrogel layer that would be formed. The higher the viscosity value, the higher the retardation effect. When the number average molecular weight increases, the viscosity also increases. The release profiles at both pH values of pH 1.0 and pH 6.8 (Figures 1 & 2) demonstrate that drug release from matrix tablets with Methocel® E5 was much faster than with all other matrix formers. This polymer, with fairly low number average molecular weight (MN 10,000), only provides weak sustained release. The matrix tablets manufactured with the high number average molecular weight polymers Methocel® K4M (MN 86,000) and Methocel® K15M (MN 120,000) provided the slowest release profiles of all matrix formers. The difference between these two polymers was not significant, especially at pH values of 6.8.

Methocel® products are nonionic products and therefore, the viscosity stays stable over a wide range of pH values (from 3 to 11). Outside this range, the viscosity is reduced (especially in the case of high number average molecular weight hydroxypropyl methyl cellulose) due to an influence on the solubility of the cellulose.[3] This explains why the release profile of the matrix tablets at pH values of 1.0 is faster than the values at pH 6.8.The release of the drug from the matrix tablets with Methocel® follows a diffusion process through the formation of gel in the tablet at high pH values, but at low pH values, diffusion is not the only mechanism involved in release of the drug.[5]

Aquacoat® ECD and EUDRAGIT® NE 30 D are inert polymers, which show a comparable retardation effect. In contrast with the HPMC formulations, the drug release happens here by diffusion and pore diffusion but not by erosion. The diffusion is affected by two factors: distribution of the polymer and the solubility of the active pharmaceutical ingredient. It was observed that the release profiles of Aquacoat® ECD and EUDRAGIT® NE 30 D are faster than the Methocel® types, but they also provide a significant retardation effect.

FIGURE 3

Compressibility Profiles of Matrix Tablets



Compressibility & Hardness

The compressibility and friability (all below 1%) were further important parameters to be compared. Tablets with EUDRAGIT® NE 30 D as the matrix former are harder than those with Aquacoat® or the Methocel® with different molecular weights (Figure 3). These higher results from EUDRAGIT® NE 30 D are because of its plastic behavior due to the high flexibility values of the polymer. The tablets were deformed until the point where they broke. In the other examples, there was less plastic behavior. From a compression force of 15 kN, "capping" is observed particularly with Aquacoat® ECD. Furthermore, matrix tablets with EUDRAGIT® NE 30 D reach a hardness maximum already at 10 kN compression force, whereas Methocel® K15M reaches this value only at 20 to 25 kN. The other different polymers types tested do not reach this maximum at all. An increase in compression force for the EUDRAGIT® NE 30 D tablets beyond 10 kN results in a slight reduction of hardness, which is caused by the elastic properties of the polymer.

Matrix Structures

The different release profiles are reflected by the matrix structures that are revealed once the incorporated drug has been dissolved. Figures 4A through 4E shows the structure of tablets after 8 hours in pH 6.8 phosphate buffer. The tablets manufactured with Methocel® E5 had dissolved completely and therefore could not be further analyzed, which confirms the weak retardation effect of this polymer in the investigated formulation (Figures 1 & 2).

The matrices made of EUDRAGIT® NE 30 D (A) show small and homogeneously distributed pores. With Aquacoat® ECD (B), there are similarly small pores, but also nonporous sections and bigger holes. The Methocel® K4M (C) and Methocel® K15M (D) matrices have a fine porous structure, as expected from the solubility in water and resulting good polymer distribution of the hydrophilic cellulose matrix formers. At high magnification, areas of undissolved Diltiazem HCl crystals could be detected in Methocel® K15M (E), which reflects the quantity of released active of 50% to 60%, after 8 hours (Figure 2).

The matrix structures obtained only correspond to the characteristics of the polymers employed, which determine the release mechanism. The inert structure of EUDRAGIT® NE 30 D and AQUACOAT® ECD causes release mainly by pore diffusion, whereas the hydrophilic hydroxypropyl methyl cellulose polymers imply drug release by swelling, erosion, and gel diffusion of the tablet. Application of mechanical stress on the "emptied" matrix tablets after the dissolution test demonstrates the different behaviors of polymethacrylate and cellulose-based matrices. Whereas the cellulose-based structures, particularly Aquacoat® ECD, are brittle, weak, and easy to break down, the EUDRAGIT® NE 30 D shows significant dimensional stability.6

CONCLUSION

According to the tests performed, all investigated polymers except Methocel® E5 are suitable for formulating matrix tablets for highly soluble drugs, such as Diltiazem HCl. Hydrophilic, high-molecular-weight hydroxypropyl methyl cellulose polymers (grades Methocel® K4M and K15M), are more effective in providing sustained release, but the influence of the pH on the viscosity directly affects the release profile of the hydrophilic matrices, which can lead to incomplete drug release in the lower gastrointestinal tract. The inert polymers EUDRAGIT® NE 30 D and Aquacoat® ECD show similar and pH-independent effectiveness, but the polymethacrylate shows better compressibility than all cellulose-based matrix formers. In summary, EUDRAGIT® NE 30 D appears to be a very favorable option when choosing a matrix former for sustained drug release.

SEM PICTURES OF MATRIX STRUCTURES AFTER 8 HOURS OF DISSOLUTION TEST IN PH 6.8 PHOSPHATE BUFFER

FIGURE 4A

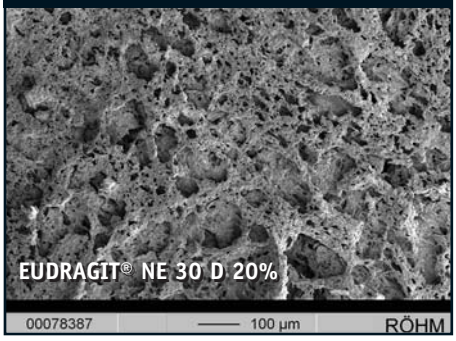


FIGURE 4B

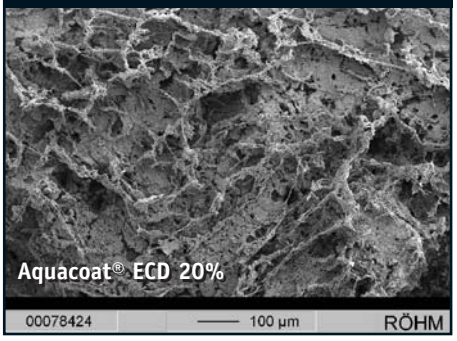


FIGURE 4C

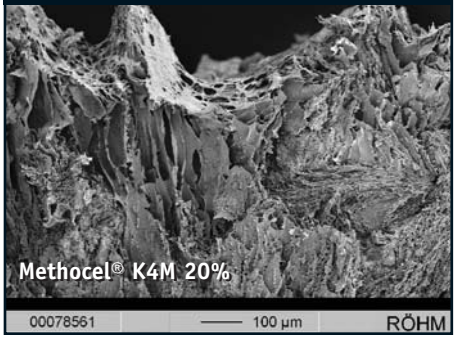


FIGURE 4D

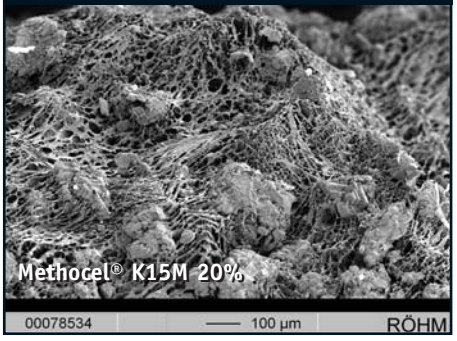


FIGURE 4E

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BIOGRAPHY

Mr. Diego Gallardo Álvarez is currently a PhD student in Pharmaceutical Technology for Degussa's business line of Pharma Polymers, one of the world leaders in the manufacturing and supplying of functional coatings for the pharmaceutical industry. Mr. Gallardo started with Degussa Pharma Polymers in May 2004 for an internship in the Pharma Polymers Technical Customer Service Department working on the manufacturing of matrix tablets by fluidized bed granulation comparing different EUDRAGIT® types with HPMC Polymers. Since May 2005, Mr. Gallardo has been focussing on dealing with matrix formulations based on EUDRAGIT® polymers in conjunction with the University of Düsseldorf, Germany. Prior to joining Degussa, Mr. Gallardo worked as a Quality Control Representative at the GMP department of Eli Lilly and within the Practices Regulatory and Quality Control departments at Roche and Medeva Pharma. Mr. Gallardo earned his degree in Pharmacy at the University of San Pablo C.E.U. and his Diploma of Advanced Studies in Pharmaceutical Technology at the University Complutense of Madrid in Madrid Spain.

BUSINESS MODELS

Financial Implications of Transitioning From a Drug Delivery to Specialty Pharmaceutical Company

By: Tim Howard

INTRODUCTION

There are few large pure-play public drug development companies. Most drug companies that have attained significant revenue and market value have done so through augmenting the drug delivery licensing model with the retention of product rights and the capture of a larger percentage of associated product revenues. During a plenary session of the recent Drug Delivery Partnership conference, the vast majority of participants indicated they had, or were in the process of, transitioning from a drug delivery company to a specialty pharmaceutical firm.

This article will examine some of the financial implications of transitioning from a pure drug delivery business model to a specialty pharmaceutical model. In this case, the transition includes the ultimate intent to sell branded pharmaceuticals to one or more medical specialties. The analysis is based upon recent financial data from three sets of public companies as described in Table 1.

The Enterprise Value (Market Capitalization – Cash + Debt) increases as a company transitions from the drug delivery to specialty pharmaceutical business model. The median Enterprise Value of the drug delivery group was under $200 million, significantly less than that of the Transition and Specialty Pharmaceutical groups, with median Enterprise Values of $1.2 billion and $3.2 billion.

Public specialty pharmaceutical companies trade at slightly higher Trailing Revenue Multiples than pure-play drug delivery companies. Comparison of EBITDA (Earnings Before Interest, Taxes, Depreciation, and Amortization) between specialty pharma and drug delivery companies is not meaningful given the fact that the majority of the drug delivery companies are operating at a loss. What is most notable however is that specialty pharmaceutical and drug delivery companies trade at Revenue Multiples that are significantly lower than Transition companies as illustrated in Figure 1.

The market appears to reward drug delivery companies that communicate their intent to transition to a specialty pharmaceutical business model. During the transition period, transition companies adopt specialty pharmaceutical SG&A (Sales, General & Administrative) cost structures. In the case of R&D expenses, the transition period is expensive and, as a percentage of revenue, dwarfs the expenditure of companies that have completed the transition as illustrated in Figure 2.

Fortunately, the public markets, at least at present, appear willing to lend money to companies in transition. The drug delivery and specialty pharma groups have median Debt/Equity ratios under 0.1, while companies in transition have a median Debt/Equity ratio of 2.5. Increased leverage is not the only source of risk that Transition companies face. Even with significant R&D expenditures, companies are still limited in the number of "bets" that they can place. In most cases, they are limited to two or three products that they can effectively carry through development to market approval. Given the probability of a product receiving FDA approval, there is great pressure on firms in transition to license or acquire late-stage

Success of the transition to a specialty pharmaceutical company depends on sound financial management and an ability to tap the equity and debt markets to fund the transition most assuredly; however, this is just the tip of the iceberg. Establishment of a strong sales and marketing function, product development and regulatory expertise, and the augmentation of traditional "sell-side" business development acumen with "buy-side" business development activities, is imperative to execute the transition.

FIGURE 1

Enterprise Value – TTM Multiple

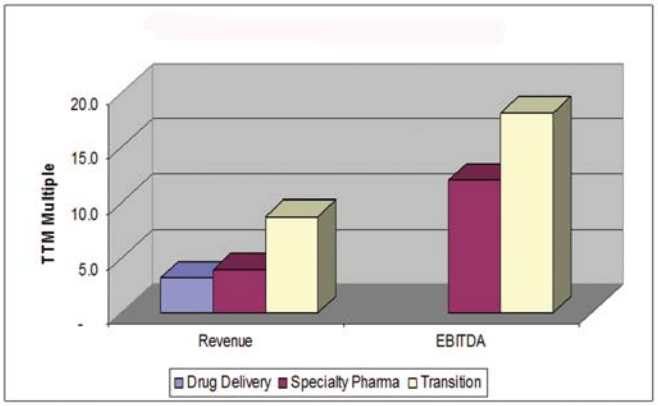


FIGURE 2

Operating Expenses

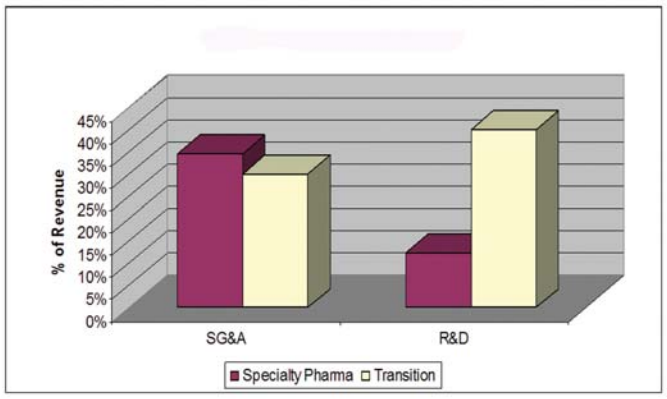


Table 1.

Drug Delivery Companies	Transition Companies	Specialty Pharmaceutical Companies
Aradigm	Alkermes Inc.	BioVail Corp
Emisphere	Bentley Pharmaceuticals Inc.	Endo Pharmaceuticals
Flamel Technologies SA	Elan	KOS Pharmaceuticals
IOMED Inc.	KV Pharmaceutical Co.	Medicis
Quigley Corp.	Nektar Therapeutics	Shire Pharmaceuticals
	SkyePharma	Valeant Pharmaceuticals

compounds that have a better than 1 in 5 chance of receiving approval.

Success of the transition to a specialty pharmaceutical company depends on sound financial management and an ability to tap the equity and debt markets to fund the transition most assuredly; however, this is just the tip of the iceberg. Establishment of a strong sales and marketing function, product development and regulatory expertise, and the augmentation of traditional "sell-side" business development acumen with "buy-side" business development activities, is imperative to execute the transition.

The transition from pure drug delivery company to a specialty pharmaceutical company is risky, however, when executed effectively provides significant returns to shareholders. Ultimately, the market rewards profitable growth. The specialty pharmaceutical group, with their median operating margin of 29%, and their ability to leverage their investment in sales, development, and regulatory expertise by in-licensing additional products, are well-positioned to deliver on that profitable growth.

BIOGRAPHY

Mr. Tim Howard leads the Life Science practice with Stonecroft Capital and has extensive transaction and management experience in the Healthcare and Life Science sectors. Stonecroft Capital is an investment bank dedicated to providing the highest quality strategic advice to growth companies with high potential. Prior to joining Stonecroft, Mr. Howard was Founder and CEO of Galt Associates, Inc., a bioinformatics firm providing solutions to leading biopharmaceutical and medical device companies worldwide. Mr. Howard has twice been selected as an Ernst & Young Entrepreneur of the Year Regional Finalist in the life sciences sector, and led his company to positions in the Deloitte & Touche National Fast 500, and Virginia Fast 50. He has led venture financing, partnering, and acquisition activities and negotiated strategic transactions with 80% of the top 20 global pharmaceutical companies. Mr. Howard currently serves as a Board Member and Advisor to numerous life science companies. His education includes a BS in Physics and Mathematics from Ursinus College, and an MBA from The Wharton School of the University of Pennsylvania.

Drug Delivery EXECUTIVE

pSivida Limited: Applying Nanotechnology to Developing Next-Generation Drug Delivery Solutions

GAVIN REZOS
CEO
pSIVIDA

PSivida is best known for developing BioSilicon, a porous, nanostructured form of silicon, as a platform for the delivery of therapeutics across a wide range of clinical applications. The company's core focus is in the rapidly growing market for new drug delivery formulations, where the value of the global drug delivery market is in excess of $66 billion, and is estimated to grow to $114 billion by 2007 (Datamonitor). Recently, pSivida acquired US-based Control Delivery Systems (CDS), Inc. for $104 million in a strategic move to reinforce its drug delivery focus and expand its presence in the key US market. CDS has a strong history of developing drug delivery devices for the back of the eye, including one product for cytomegalovirus retinitis, a blinding eye disease primarily afflicting late-stage AIDS patients, and another that is currently under review by the FDA for posterior uveitis. Drug Delivery Technology spoke with pSivida's CEO Gavin Rezos about pSivida's growth, its reasons for this acquisition, and how the enlarged company plans to become a leading global healthcare company.

"Furthermore, our ability to control the structure of BioSilicon means we can develop formulations with drug-release kinetics tailored to specific clinical requirements, including those that produce zero-order release kinetics with minimal or no burst-release effects, which could be crucial in optimizing the therapeutic profile of certain drugs."

Q: Before we go into the reasons why pSivida acquired CDS, can you provide a potted history of the company and its innovative nanotechnology?

A: pSivida was founded in 2000 to research, develop, and commercialize medical applications from its proprietary BioSilicon nanotechnology platform. This platform was developed in the UK in the mid to late 1990s at QinetiQ, a leading international defense, security, and technology company, by Professor Leigh Canham, our Chief Scientific Officer and a leading authority on nanostructured silicon.

Prior to the CDS acquisition, our corporate headquarters was in Perth, Australia, our main R&D facility in Malvern, UK (next door to QinetiQ), and a clinical trials team in Singapore.

The principle of pSivida's BioSilicon is very simple; we fill silicon particles with holes at the nano level (one nanometer is one billionth of a meter or about 1:100,000th the width of a human hair) to create a honeycomb matrix. By nanostructuring, we can fine tune a number of the key material properties of semiconductor silicon, eg, its optical, mechanical, and thermal properties, and very importantly, create the additional benefit of biodegradability in the human body. We load this honeycomb matrix with drugs, which can be

released at controlled rates over hours, days, weeks, or months inside the human body.

The rate of drug release is governed by the rate at which the BioSilicon degrades, and these rates can be controlled by altering the physical characteristics of the nanostructured silicon during the manufacturing process, ie, particle size, porosity, and size of the pores.

Q: So why silicon, and what medical applications have you identified for BioSilicon?

A: First, Silicon is the earth's third most abundant element, being 28% of the earth's crust. BioSilicon derives from low-cost semiconductor silicon, which has been used for more than 40 years in the electronics and semiconductor chip industry; therefore, there is a wealth of knowledge about its processing, purification, and scale-up manufacture.

Our own safety and toxicology studies, as well as human clinical data, have demonstrated that BioSilicon has an excellent safety profile, as it biodegrades into silicic acid, the natural form of silicon absorbed from every day foodstuffs, such as rice, beer, and bread.

As well as being biocompatible and biodegradable, BioSilicon is extremely versatile and can be processed into many different forms, including microparticles, membranes, woven fibres and fabrics, micromachined implants, and microdevices. We have a comprehensive patent portfolio covering the medical use of BioSilicon in or on the body, and while pSivida's core focus is on developing applications for the targeted and controlled release of therapeutics, we also believe that BioSilicon has great potential in the areas of orthopaedics, wound healing, and tissue engineering. Our strategy is to out-license the technology in these areas.

Q: Why have you decided to focus on the controlled delivery of therapeutics?

A: The development of innovative technologies to improve the delivery of therapeutics is of significant interest to the pharmaceutical industry as they can be used to extend product revenue lifetimes. For the patient, better targeted and controlled delivery vehicles or formulations can improve things like bioavailability, therapeutic efficacy, and compliance while reducing adverse side effects resulting from poor targeting or high dosing of certain drugs to achieve therapeutic levels.

For example, it is estimated that 40% to 50% of all NCEs have solubility issues, whereas 10% of marketed drugs face efficacy issues relating to poor solubility and bioavailability. These drugs alone had sales of an estimated $72 billion in 2003, according to Technology Catalysts.

From our perspective, the drug delivery market is growing rapidly and is estimated to reach nearly $114 billion by 2007. The unique properties of our BioSilicon technology lead us to believe that pSivida can become a significant player in this market.

Q: What particular benefits do you believe BioSilicon can offer?

A: BioSilicon has many advantages for the controlled release of therapeutics in addition to those mentioned earlier. For example, BioSilicon microparticles can be loaded very efficiently with drug, with drug loading being modulated by controlling the level of porosity; modifying the pore size also means it can carry a wide range of therapeutic molecules from small molecules to larger peptides, including those that are either hydrophobic or hydrophilic.

The efficient delivery of hydrophobic drugs is of enormous importance to the pharma industry as it significantly affects drug solubility, and consequently bioavailability and clinical efficacy. pSivida has demonstrated in preclinical research that many poorly water-soluble drugs can be formulated using BioSilicon (and their solubility improved), and currently, we are evaluating compounds for a number of pharma and biotech companies in this area.

Furthermore, our ability to control the structure of BioSilicon means we can develop formulations with drug-release kinetics tailored to specific clinical requirements, including those that produce zero-order release kinetics with minimal or no burst-release effects, which could be crucial in optimizing the therapeutic profile of certain drugs.

Q: Can you tell us about the development of your lead product BrachySil?

A: BrachySil is a novel brachytherapy product developed using BioSilicon, which is in Phase IIb clinical trials for the localized and targeted treatment of inoperable liver cancer. We are also preparing to initiate Phase IIa trials with BrachySil in pancreatic cancer. All going well, we would look to submit regulatory applications for BrachySil in liver cancer in 2007.

Clinical trial data have shown BrachySil to be safe and well-tolerated. While efficacy was not the primary endpoint of these trials, we were very excited to find that BrachySil also caused considerable regression of tumors in some patients (including 100% regression in some smaller tumors), and the purpose of our new Phase IIb trials is to find the optimal dose.

A key advantage of BrachySil is that it is administered as a suspension directly into the tumors using a fine-gauge needle, while the patient is under local anaesthetic. The short effective range of 32P of 2 to 3 cm means that the procedure can be performed without excessive shielding (just using a shielded syringe) and with accurate targeting, which avoids damage to healthy surrounding tissues.

Q: You have also just signed your first commercial licensing deal for BrachySil, can you tell us briefly about that?

A: The licensing deal is with Beijing Med-Pharm for the development, marketing, and distribution of BrachySil in China, the world's fastest growing market for pharmaceuticals and the country with the highest incidence of the type of liver cancer BrachySil is in development to treat.

The deal gives us more than $2 million in upfront and milestone payments and royalties of up to 30% depending on sales. We believe this deal validates the commercial potential of BrachySil and will serve as a robust platform for further licensing agreements for BrachySil in other territories.

Q: Regarding the CDS acquisition, you have recently acquired CDS for $104 million, can you tell us a little bit about this company?

A: Control Delivery Systems is a private US company based in the Boston, MA, bioscience hub. CDS designs and develops sustained-release drug delivery implant devices for ophthalmologic conditions and has two launched products [Retisert™ for the treatment of uveitis (inflammation at the back of the eye) and Vitrasert™ to treat AIDS-related CMV retinitis] currently marketed by Bausch & Lomb and bringing in revenues. CDS has a second-generation product, Medidur, in Phase III clinical trials and is expected to reach the market in the next few years.

Q: Could you also explain the strategic importance of this deal?

A: This deal is highly significant for pSivida. For more than 1 year, we have been looking for a US-based private company with state-of-the-art facilities in the US and a staff with strong clinical, regulatory, and development expertise in the drug delivery area and with experience with the FDA.

The key strategic aims for conducting this acquisition were to increase our resources so we could speed up the development of our BioSilicon platform; accelerate the growth of a diverse portfolio of innovative drug delivery products and technologies; and increase our visibility in the US to potential partners, investors, and skilled employees with the vision of creating a truly global bio-nanotech company.

CDS fitted the bill perfectly. It is revenue-generating, has a valuable market for its existing products and product pipeline, and has technologies we can combine with pSivida's to potentially create innovative drug delivery technologies.

Q: So to conclude, where do you see pSivida in 10 years?

A: We believe the future of drug delivery is at the nanoscale, and for a company as ambitious as pSivida, this opens up enormous and valuable opportunities. To be at the forefront of this area, companies will need great technology, specific and sought-after expertise, a strong development track record, and access to sufficient future capital. We believe that pSivida through its own achievements throughout the past few years and now in combination with CDS, will be among the leading companies in this field.

In 10 years, I expect that pSivida will be a well-recognized global company developing a range of products designed to improve the delivery and efficacy of therapeutics. Our products will be developed from proven and proprietary platforms, including BioSilicon, in partnership with leading pharmaceutical companies across a broad range of clinical areas. ♦

Drug Delivery Showcase

New DDS Facility

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

Smart Pump Technology

Smart pump technology is especially effective when accurate IV medication administration is critical. The Medfusion™ 3500 Syringe Pump is designed with PharmGuard™ Medication Safety software, an infusion system using specific configuration profiles, a drug library of more than 4,000 entries, over 100 dosing units, and safety dose limits on all infusion parameters to reduce medication errors. The smart pump's rapid occlusion detection technology with FlowSentry™ offers many pressure-related safety features, and its graphic display of pressure trend allows for earlier clinical intervention. These pressure features are available without the use of an expensive, cumbersome dedicated set. The Medfusion™ 3500 Syringe Pump imports and exports data and protocols, and may be adapted and customized to interface with your bedside environment. For more information, visit **Smiths Medical** at **www.smiths-medical.com.**

Sustained-Release Technology

Oakwood Laboratories is all about the practical application of sustained-release drug delivery technology for parenteral pharmaceuticals. The company has a unique microsphere-based technology platform it's employing to develop drugs for partners as well as itself. Oakwood's proprietary CHRONIJECT™ technology provides an adaptable, cost-efficient, and easily scaleable system for the injectable controlled release for multiple drug classes. A distinct benefit is its ability to offer customizable release profiles, as well as control of the duration of delivery. Oakwood is actively seeking collaborations with companies that have currently marketed products or with products in development that could be enhanced by a controlled-release dosage form. For more information, contact **Oakwood Laboratories** at (440) 359-0000 or visit **www.oakwoodlabs.com.**

Inhaler Testing

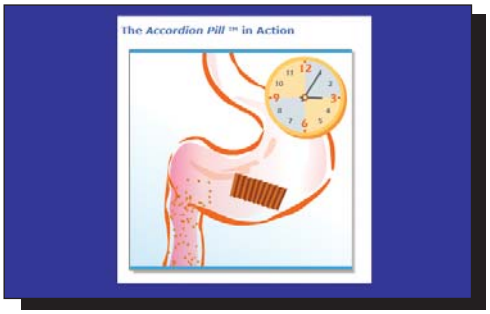
ASTECH are experts in the implementation of automated testing for MDI and DPI devices. The company has extensive experience, working with most of the world's leading pharmaceutical companies to develop solutions for R&D and high-volume QA batch-release testing. ASTECH's in-depth knowledge of the requirements of the inhalation industry allows it to develop advanced automated systems, previously not available to the market. From Emitted Weight or Dose Testing, through Cascade Impaction, to Vision Analysis of delivered dose, ASTECH can provide the right solution to meet your exact requirements. ASTECH's systems provide the capability for true unattended operation. Its systems are simple to use and its dynamic scheduling and state engine control software provides a highly versatile environment for operator control and data analysis. For more information, visit **AstechProjects** at **www.astechprojects.com.**

Drug Delivery Showcase

Liposomology / Drug Delivery

Polymun Scientific provides contract development and manufacturing and creates liposomal formats of drugs for partners. Revenues are invested in proprietary products and further development of technology platforms. R&D projects and technologies are open for co-development and licensing. Liposomes protect, transport, and release your drug at the right place and time. By this, a reduced dose achieves better efficacy and avoids side effects with a non-invasive application. Polymun's technology enables the industrial realization of pharmaceutical and cosmetic products for liposomal drug formats. The production technology is suitable for a broad range of substances formulated by passive entrapment, active loading, or membrane incorporation. Main characteristics include: Scalability; Sterility; Homogeneous, Uniform Vesicles; Entrapment of Several Product Classes with High Efficiency; Batch-to-Batch Consistency; and Mild Procedure -Stability. For more information, contact **Polymun Scientific** at **www.polymun.com.**

Gastric Retention Dosage Form

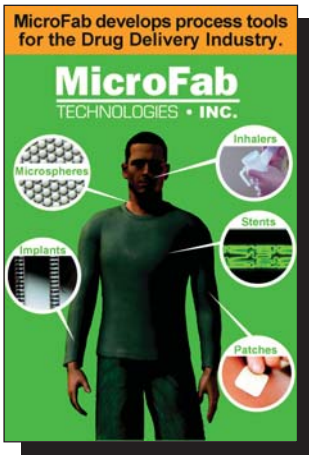


Intec Pharma's Accordion Pill™ (an innovative Gastric Retention Dosage Form) is an expandable, biocompatible, and biodegradable drug-polymer matrix. Delivering its drug payload to the upper gastrointestinal tract, the Accordion Pill achieves high gastric retention and proven increased bioavailability. The matrix is folded like an "accordion" into a standard-size gelatin capsule. The matrix is composed of synthetic and biodegradable polymers that are categorized as GRAS (Generally Recognized As Safe) materials by the FDA or are recognized as inactive ingredients by the FDA. By its ideal controlled-release approach, the Accordion Pill can significantly reduce adverse drug reactions and consequently enhance patient care by significantly improving compliance via less frequent dosing. Better bioavailability will deliver enhanced efficacy and reduce toxic side effects. For more information, visit **Intec Pharma** at **www.intecpharma.com.**

Transdermal Therapy

Hisamitsu Pharmaceutical boasts an impressive line of products developed to bring the transdermal therapeutic system to diverse applications. Its SALONPAS series, for example, features patches of various types in order to suit many different requirements in pain relief. In its line-up of medical products, the company offers the Sector, Japan's first external pain relieving drug containing ketoprofen, and Mohrus, the world's first transdermal patch containing ketoprofen. Mohrus Tape, Japan's first transdermal patch to be approved for the treatment of back pain, Vesicum, the company's original formulation containing ibuprofenpiconol, and ESTRANA, transdermal therapeutic estradiol drugs, are also well known. Our over-the-counter products include a range of external pain-relieving patches and aerosols led by the popular SALONPAS line. For more information, visit **Hisamitsu** at **www.hisamitsu.co.jp.**

Ink-Jet Technology & Services



MicroFab Technologies, Inc., develops ink-jet microdispensing equipment and processes for the drug delivery industry. The technology enables precise digital control for microdispensing applications ensuing unsurpassed accuracy and repeatability. Printing drugs and drug-polymer combinations in complex patterns are characteristics of the technology. Products that can be manufactured by ink-jetting include drug-loaded microspheres, drug-eluting stents, implants, metered inhalers, and transdermal patches. MicroFab combines an in-depth understanding of the science of ink-jet printing with proven manufacturing know-how. Because of this, you will benefit from MicroFab's microdispensing equipment and full laboratory service designed to fit even your most stringent requirements. For more information, contact **MicroFab Technologies, Inc.**, at (972) 578-8076/ext. 11 or visit **www.microfab.com.**

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Knowledge, Comprehension, Insight, Awareness & Appreciation

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.

When you type the word "understanding" into your computer and then hit the thesaurus key, you get these words (see title) plus many more. This brings a question to mind: do executives really understand what goes on inside of their companies, especially senior executives? I'm not referring to people like our friends at Enron, but instead to those executives like you and me.

We have *Knowledge, Comprehension, Insight, Awareness, and Appreciation* for the people we work with, but this is primarily for those whom we work with everyday. As an executive, you know your peers, your subordinates, their subordinates, and others in your office, but do you really understand completely what is going on inside your company? Let's take a manufacturing company that I know of as an example of what I am referring to.

The company has a headquarters in the northeast, 5 manufacturing plants in the US, 11 distribution centers (DCs) across the country, and the total headcount for the company is 1,200. Approximately 75 people are at the headquarters, 120 are around the country in sales, and the remainder of the people are in the plants and the distribution centers. Okay, here is the math whiz at work.

Of the 1,200 people who work for this company, 1,005 work in the plants and DCs or 84% of the total. How well do you think the senior executives know the 84% of the people that I am referring to? They know the plant and DC management to varying degrees, but no one much beyond that. I asked the CEO of this company what he does when he visits the plants and DCs, which is not very often. He told me that he meets with the management of these facilities and then may or may not walk around with the facility management.

How well do you think he "understands" what the vast majority of the people at this company go through everyday to manufacture quality products and then ship them correctly and on time? He doesn't, although he talks frequently about the company's team culture and their family approach. Can you imagine a family with 5 children and the parents only have time for, to understand, and have empathy for 1 child and not the other 4? That means 80% of the children are ignored. Same thing with this company. The executives ignore 84% of the family.

I have read in the newspaper more then once about one particular telecommunications company CEO expressing his great concern for "his people" and how grateful he is to the "the working people." I wonder if he has ever spent time hanging off of a utility pole in 10 degree weather at night trying to restore service? Or living from pay check to pay check trying to pay bills? You bet.

I think that it is important for executives to travel to their facilities and really learn to "understand" what the majority of their people go through every day to earn a living and support the company. Some companies send their executives out to their plants to work on the production lines and in the DCs. They spend several days learning to understand what the manufacturing distribution people do everyday. I tried this once but the manufacturing people told me that I would either get hurt and kill their record for "days without a reportable injury" or I would screw up the production line and bring their quality and efficiency numbers to a new low. Thanks gang!

What I do instead is go to the plants and DCs for my quarterly management meetings, then spend a great deal of time walking the floors talking to the people, complementing their work, and I put at least 2 hours aside for hourly employees to meet with me individually to tell me what I need to know. Sometimes there are personal issues, which is fine, but primarily they tell me things that will improve the company.

I think that we can all gain *Knowledge, Comprehension, Insight, Awareness, and Appreciation* for our people if we would just take the time to communicate and understand what they go through every day. It will make you a better executive and help you to help the company. ♦

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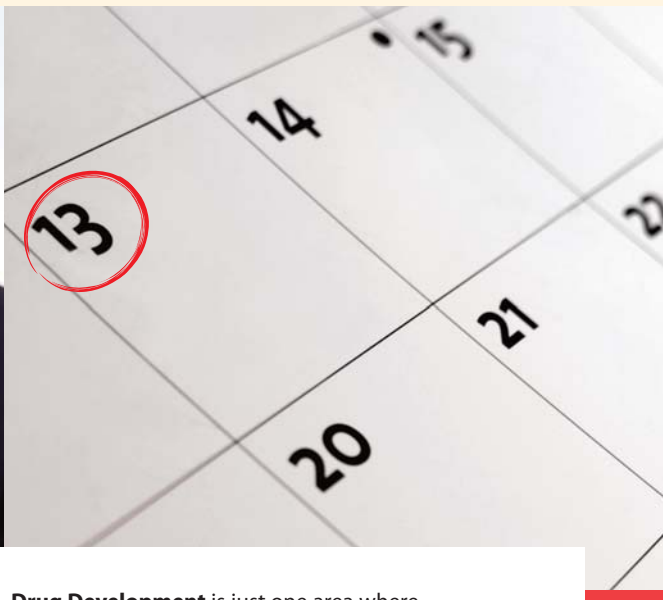

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